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HAY-FEVER AND HAY-FEVER POLLENS*

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NEW ORLEANS

The causative relationship of pollens to hay-fever has become so well established that it appears almost superfluous to offer additional evidence. The experience of the past year in the correspondence of the American Hay-Fever-Prevention Association, however, has shown that there are still many who doubt that hay-fever is caused by pollen, and that there are many more who believe that pollen is only one of the exciting causes of this disease. Under the circumstances, a brief review of the most important proofs of this relationship will be of advantage.

In hay-fever, as in many other pathologic conditions, we have to consider, in addition to the exciting cause, the predisposing factors. In the greater portion of the United States there are at certain seasons many pollens in the atmosphere, which are inhaled by all in the course of normal respiration Of this number, only a certain proportion of persons (about 1 per cent. in most states) develop hay-fever, the remainder apparently not being inconvenienced by these pollens. Those who develop hay-fever evidently have some predisposition or lower resistance, which causes them to develop hay-fever while others are not affected. That this predisposing factor is still unsettled is evidenced by the fact that in the questionnaire recently sent out by the United States Public Health Service[1] in Louisiana, fifty-four physicians gave forty-eight different predisposing causes for hay-fever.

EXPERIMENTAL HAY-FEVER

The reaction of hay-fever, in no way differing from the normal attack at the usual season, except that the length and degree of the reaction is under control, may be artificially produced at any time. In the biologic laboratory of the American Hay-Fever-Prevention Association, pollens of all the most important hay-fever plants are kept in stock, so that the effect of the various hay-fever pollens may be accurately compared.

* Received for publication Jan. 3, 1917.

1. Scheppegrell, W.: Hay-Fever in Louisiana, New Orleans Med. and Surg. Jour., October, 1916.

In producing an artificial attack of hay-fever it should be understood that the pollens are the male elements of phaenogamous or flowering plants, and are, therefore, incapable of reproduction in the nostrils or tissues of hay-fever subjects, differing in this way from infection by bacterial micro-organisms. On this account, an artificially-produced

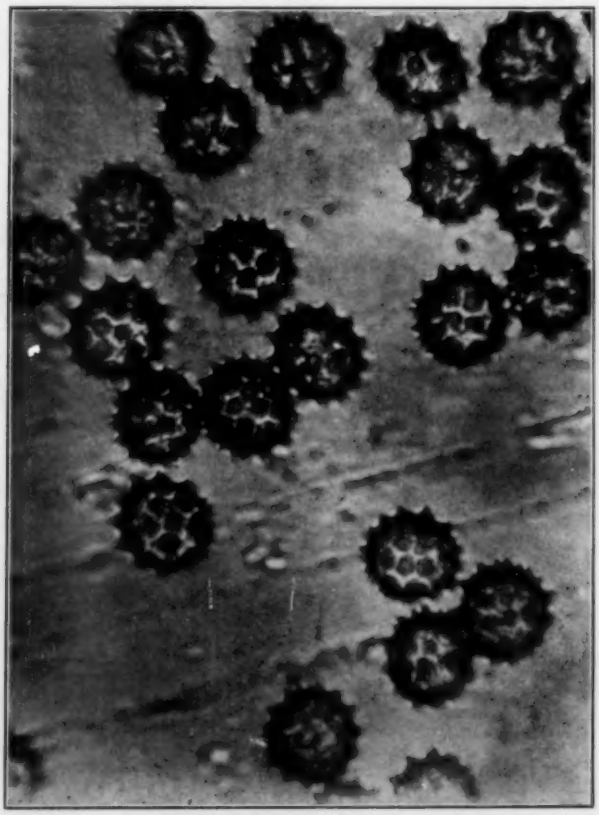

Fig. 1.—Pollen of bastard feverfew (*Parthenium hysterophorus*). The length of the spicules causes mechanical irritation of the nostril. × 1,000 diameters. (The photomicrographs illustrating this article were prepared in the biologic laboratory of the American Hay-Fever-Prevention Association.)

attack depends on the amount and strength of the pollens used or their extract, and, if the reaction is developed outside of the usual hay-fever season of the subject when there are no toxic pollens in the atmosphere, the length and degree of the attack may be accurately controlled.

This explanation is made in view of the repeated inquiry as to whether an artificially-produced reaction will not result in an attack of hay-fever of the usual duration. That this will not be the case will be understood when the nature of this process is explained.

REACTION FROM HAY-FEVER POLLENS

The reaction from hay-fever pollens may be divided into the direct and indirect effect. The former is due to the direct irritating effect of the pollen on the nasal mucosa. This may be mechanical, as with many

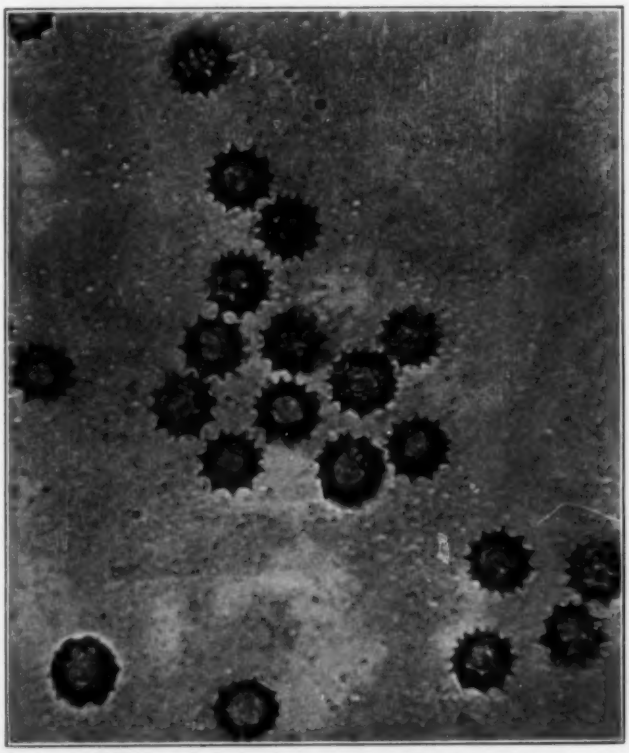

Fig. 2.—Pollen of sneezeweed (*Helènium quadridentata*). Also has marked spicules. × 500 diameters.

of the spiculated pollens. In some of these, as in the bastard feverfew (*Parthenium hysterophorus,* Fig. 1) and the sneeze weed (*Helenium quadridentata,* Fig. 2) the spicules are so prominent that they produce a reaction, due to the mechanical impact, even in persons who are not susceptible to hay-fever. This effect is immediate, and, in persons not

subject to hay-fever, is relieved as soon as the irritating pollens are discharged.

The primary effect may also be physiochemical in its character. In the wormwoods (*Artemisias*), which replace the ragweeds (*Ambrosias*) in the Rocky Mountain and Pacific states, the primary effect of the pollens, which are smooth, is as rapid and much more violent than with the spiculated pollens. The examination under the microscope shows that as soon as this variety of pollen comes in contact with the nasal secretion or the normal saline solution, it immediately ejects a portion of its contents from one or all of the three points of intersection of its three-lobed extine (Fig. 3). This fluid, which does not respond to the Lugol solution for starch, is a toxalbumin markedly irritating to the nasal mucosa, which explains the rapidity and extent of the local irritation.

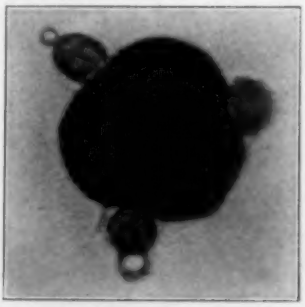

Fig. 3.—Pollen of wormwood (*Artemisia absinthium*). Showing effect of the absorption of nasal mucus. × 1,000 diameters.

The degree and duration of the primary effect of pollens is influenced by the irritability of the nasal mucosa of the patient. In some cases an intumescence of the nasal mucosa results which causes occlusion of the nostril and retention of the pollens, thus favoring absorption of their toxalbumins. In others, pollen causes a free discharge of a secretion which contains but few mucous corpuscles, but the usual salts of the nasal secretion (Fig. 4). The bacteriologic examination of a succession of hay-fever patients showed but slight variation from the bacteria found in the mucous secretion of the normal person. Pollen, however, is found in a large proportion of cases (Fig. 5) if the examination is made of the nasal discharge in the morning after the secretions have accumulated during the night.[2]

The indirect effect is due to the absorption of some portion of the pollen contents — the toxalbumins — under the influence of the nasal

2. Scheppegrell, W.: Ragweed Pollen in the Nasal Secretion of Hay-Fever Cases, Med. Rec., New York, October, 1916.

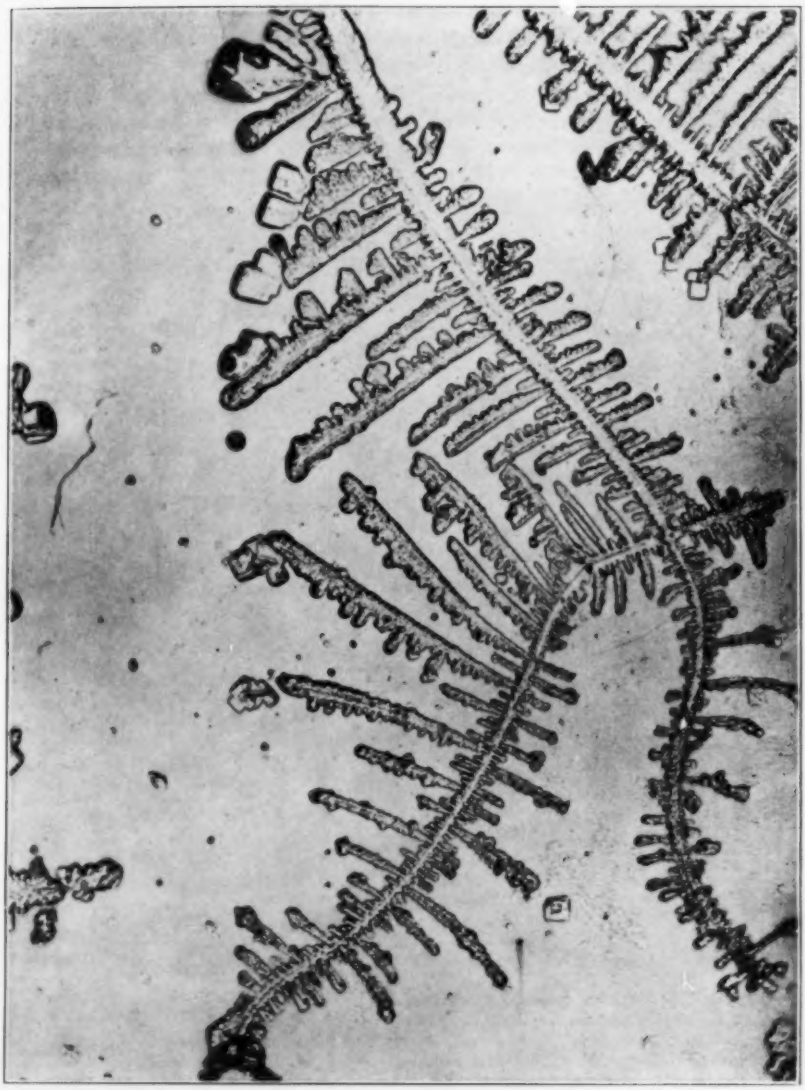

Fig. 4.—Nasal secretion of hay-fever patient showing preponderance of the salts and small number of mucous corpuscles. × 125 diameters.

secretion. This is demonstrated by the fact that the aqueous extract of toxic pollens produces a reaction in hay-fever subjects similar to the pollens themselves. This is characteristic of all hay-fever pollens. In the pollen of the *Gramineae,* in which the local (direct) reaction is slight, it is the principal cause of the hay-fever. Even in pollens in which the direct effect is marked (*Ambrosias, artemisias*) the absorption of the proteins is the important factor which prolongs the attack.

Fig. 5.—Pollen of common ragweed (*Ambrosia elatior*) in the nasal secretion of a hay-fever patient. × 250 diameters.

HAY-FEVER POLLENS

While pollens are generated by all the members of the phaenogamous plants, only those which are wind pollinated need be considered in connection with hay-fever. While there are many plants whose pollen may cause the hay-fever reaction when applied to the nostrils,

only pollens which float in the air and can reach the nostrils in the course of normal respiration are responsible for true hay-fever. In the selection of hay-fever plants it is, therefore, important first to decide that they are wind pollinated,[3] as the pollens of these plants only are found in the air.

As a rule, this may usually be inferred from the appearance of the plant. Attractive flowers and perfumes are characteristic of insect-pollinated plants and the presence of these is usually sufficient to eliminate them from the list of wind-pollinated plants, as in the case of the roses and golden rods.

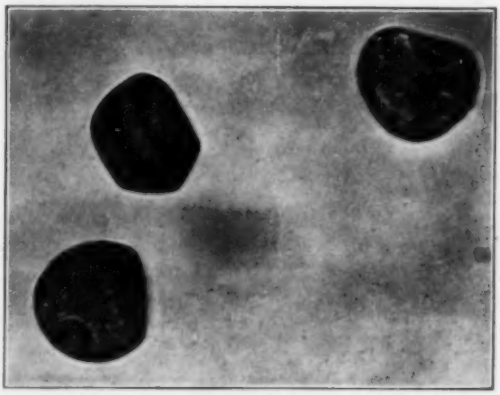

Fig. 6.—Pollen of plume grass (*Erianthus compactus*). × 500 diameters.

The absence of attractive flowers and perfumes is characteristic of the hay-fever weeds, as in the case of the ragweeds (*Ambrosias*), wormwoods (*Artemisias*), cockleburs (*Xanthiums*), careless weeds (*Amaranths*), and the grasses (*Gramineae*).

The failure to limit the classification of hay-fever plants to those that are anemophilous, or wind pollinated, has resulted in the inclusion of many plants which are entirely harmless from a practical standpoint. In spite of the clearness of this principle, we are constantly receiving lists of hay-fever weeds from all parts of the United States which include the roses, golden rods, resin weeds and other insect-pollinated plants.[4]

3. The anemophilometer, an instrument for testing the wind-pollination of plants, has been devised by the Research Department of the American Hay-Fever-Prevention Association. William Scheppegrell, Scientific American, October, 1916.

4. Even in technical books published in the last two or three years, such plants as the evening primrose, chrysanthemum, aster, lily of the valley, honeysuckle and other insect-pollinated plants are described as furnishing the toxic pollens of hay-fever.

THE POLLENS OF SPRING HAY-FEVER

From a test of many hundreds of pollens in our biological laboratory, the principal hay-fever plants have been selected. For the early type of hay-fever, the chief causes are the grasses (*Gramineae*), the special varieties varying according to climatic conditions (Fig. 6). This applies to all portions of the United States. The spring cases of hay-

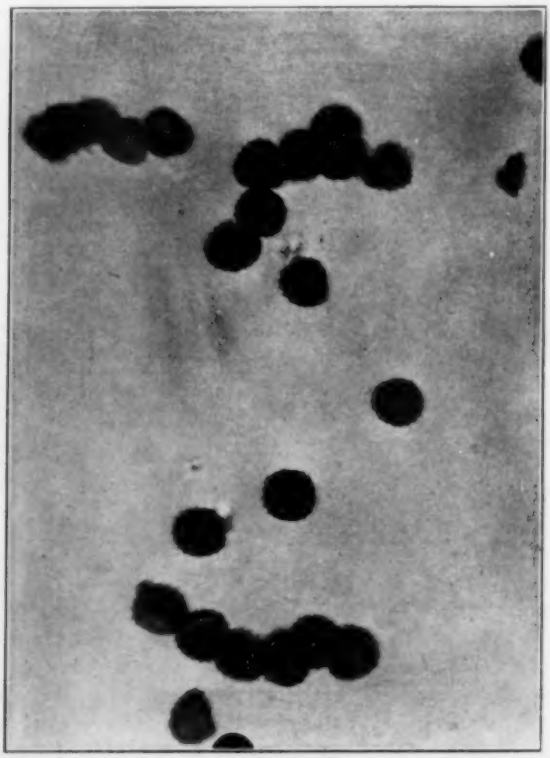

Fig. 7.—Pollen of common ragweed (*Ambrosia elatior*). The principal cause of fall hay-fever. × 500 diameters.

fever are also influenced by other wind-pollinated plants such as the amaranths (*Amaranthus*), docks (*Rumex*), and chenopods (*Chenopodium*), which, however, are, in the aggregate, of much less importance both from the standpoint of reaction and geographical distribution.

THE POLLENS OF FALL HAY-FEVER

The fall hay-fever, east of Kansas, is caused by the common ragweeds (*Ambrosia elatior*, Fig. 7), this being replaced in moist regions by the giant ragweed (*Ambrosia trifida*).[5] These cases are also affected by the pollens of the marsh elder (*Iva ciliata*) and cocklebur (*Xanthium canadensis*, Fig. 8), these, however, being of minor importance.

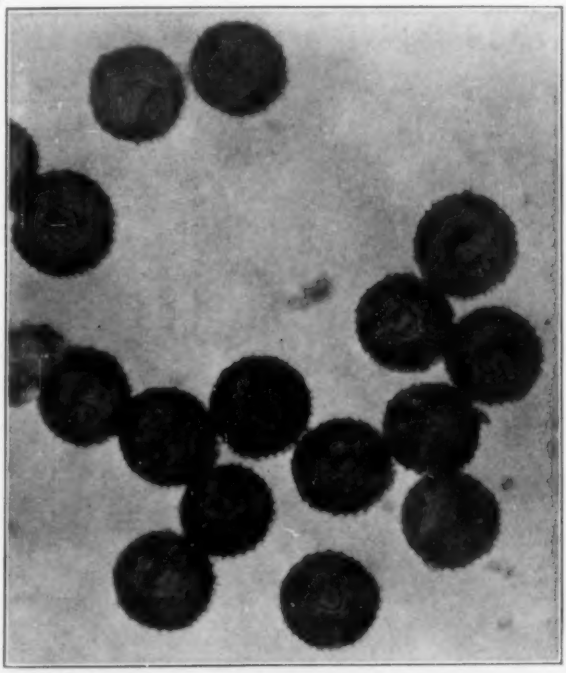

Fig. 8.—Pollen of cocklebur (*Xanthium canadensis*). A cause of fall hay-fever of minor importance, partly because it is less toxic than the common ragweed and also on account of its more restricted potential area. × 500 diameters.

In the Pacific and Rocky Mountain states, the ragweeds are replaced by the wormwoods (*Artemisias*, Fig. 9), the rough bur elder (*Iva xanthiifolia*), the *Gaertnerias* and the western ragweed (*Ambrosia psilostachya*).

ATMOSPHERIC POLLEN PLATES

Atmospheric pollen plates are prepared by applying a thin layer of glycerin to the central square inch (25.4 mm.) of an ordinary microscope slide. We have tried various combinations but have found the

5. Scheppegrell, W.: Hay-Fever and Its Prevention, U. S. Pub. Health Rep., July 21, 1916, p. 1907.

pure glycerin, thoroughly applied to the glass which has been previously cleansed with alcohol, to be the most practical. In extremely moist weather, when the glycerin deliquesces too rapidly, we substitute a layer of boiled linseed oil.

We have tried various forms of apparatus for the purpose of having these plates always at right angles to the direction of the wind. While this furnishes useful statistical data, the complicated construc-

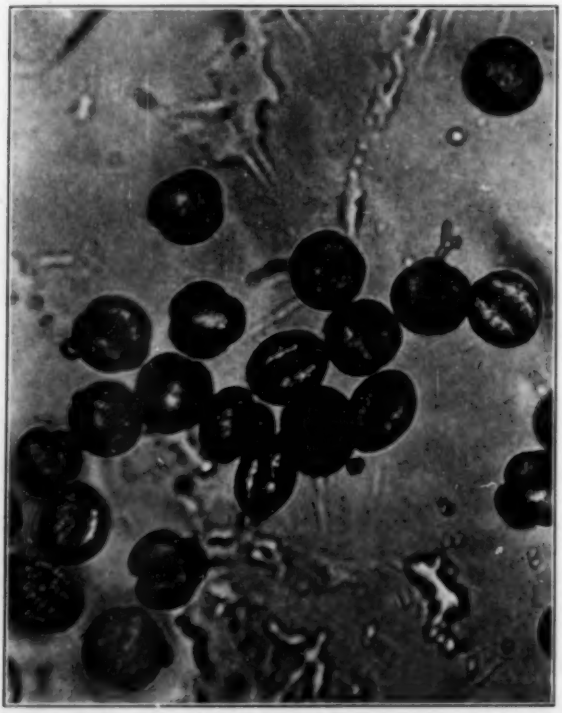

Fig. 9.—Pollen of wormwood (*Artemisia heterophylla*). One of the principal causes of fall hay-fever in the Pacific and Rocky Mountain States. × 500 diameters.

tion gives it a limited range. For practical purposes, the atmospheric pollen plates are simply exposed to the wind at the residence of the patient or at the special stations.

After twenty-four hours exposure, these plates are examined under the microscope, with the aid of the mechanical stage, so that the whole surface can be traversed. A low power (125 diameters) is sufficient for traversing the slide, and when a pollen grain is found, a high power (500 diameters) is used for its identification.

By the injection of a drop of Lugol's iodin solution, the count is simplified, as the grass pollens, which are stained blue-black, can be easily distinguished from other pollens which are usually stained brown.

After the pollens have been counted, they are reduced to the number per square centimeter, as our unit is the number of pollens per square centimeter for twenty-four hours.

As the object of the pollenometric records is to determine the amount of pollen in the air, a working formula has been prepared by means of which the number of pollen grains per cubic square yard of air may be determined from these plates.

NUMBER OF POLLEN IN THE AIR[6]

The number of pollen grains dropping on a given surface, for example, a plate, depends only on the number per unit volume of the air and velocity of fall of the pollen grains.

This means that unless the plate is inclined at an appreciable angle, for example, 15 or 20 degrees, with the direction of the wind near the plate, the number of pollen grains dropping on the plate is independent of the wind velocity, other factors, such as the number per unit volume of air, being constant. The number of pollen grains in the air, however, bears a direct relation to the velocity of the wind.

If the pollen grains fall with a velocity of v feet per second, and there are in the air n per cubic yard, the total number N falling on a square centimeter in t hours is given by the formula

$$N = 0.143 \times n \times v \times t$$

and

$$n = \frac{7 \times N}{v \times t}$$

For example, if the diameter of the grain is 0.020 mm., $v = 0.16$ feet per second. If N' pollen are gathered in twenty-four hours

$$n = \frac{7 \times N}{0.16 \times 24} = 1.8\ N'$$

If N' represent the number of pollen grains gathered per square centimeter on an atmospheric-pollen plate in twenty-four hours and the number of pollen per cubic yard is represented by n, the following are the numbers by which N' is to be multiplied to give n, for the pollen of different diameters:

Diameter = 10 microns, n = 7.3 N′
Diameter = 15 microns, n = 3.2 N′
Diameter = 20 microns, n = 1.8 N′
Diameter = 25 microns, n = 1.2 N′
Diameter = 30 microns, n = 0.8 N′
Diameter = 40 microns, n = 0.45 N′
Diameter = 50 microns, n = 0.30 N′
Diameter = 60 microns, n = 0.20 N′
Diameter = 70 microns, n = 0.15 N′
Diameter = 80 microns, n = 0.12 N′

To obtain the number of pollens per kilo-liter, divide the number N', per cubic yard by 1.3.

6. Report of Prof. J. H. Clo, Department of Physics, Tulane University, New Orleans.

In October, 1916, the pollenometric records indicated nineteen common ragweed pollen grains for twenty-four hours. As this pollen has a diameter of 15 microns, we multiply the number of pollen by 3.2 of the formula, which shows that there were sixty-one pollen grains in each square yard of air on that date.

NASAL FUNCTION IN ARRESTING HAY-FEVER POLLENS

Several clinical tests were made in order to determine what percentage of atmospheric pollen grains are arrested in the nostrils. The conformation of the nasal passages is especially adapted not only for warming and moistening the inspired air, but also for arresting mechanical impurities, the tests showing that over 70 per cent. of the inhaled hay-fever pollen grains are arrested in the nasal passages.

Aug. 12, 1916, all of the nasal secretion of a hay-fever patient for eight hours was collected. As the patient slept in an open sleeping porch, the inhaled air contained the average number of aerial hay-fever pollens of that date and location. The number of pollen grains which the secretion contained were then counted and found to be 56. On the same date, the pollenometric record showed 10 giant ragweed (*Ambrosia trifida*) pollen grain for twenty-four hours. As these pollen grains have a diameter of 20 microns, the number per cubic yard was found to be 18 according to our table of atmospheric pollens. As the volume of air (tidal) for eight hours' respiration was 4.28 cubic yards, the patient had inhaled (4.28×18) 77 pollen grains during the eight hours. As 56 pollen grains were found in the secretion, it demonstrated that the nostrils had arrested about 73 per cent. of the grains which the patient had inhaled.

THE POLLENS OF HAY-FEVER VERIFIED BY THE ATMOSPHERIC POLLEN PLATES

The pollens responsible for hay-fever were verified by the atmospheric-pollen plates, which our research department exposed during the whole of the past hay-fever season. During the prevalence of the spring hay-fever, these plates, which were exposed at various stations and also near the residences of the hay-fever patients, invariably showed the grass pollens with a small percentage from other wind-pollinated plants such as the docks, amaranths and chenopods. The number of pollen grains deposited bore a definite relation to the intensity of the hay-fever attack.

In the fall hay-fever season the pollenometric records showed the presence of the ragweed almost exclusively (Fig. 10). August 15, the grasses had practically completed their pollination and their pollens had

almost disappeared from the air, as shown by these plates. The patients who were affected with the grass pollens had ceased to suffer from hay-fever, except those patients who were sensitive to both the grass and ragweed pollens.

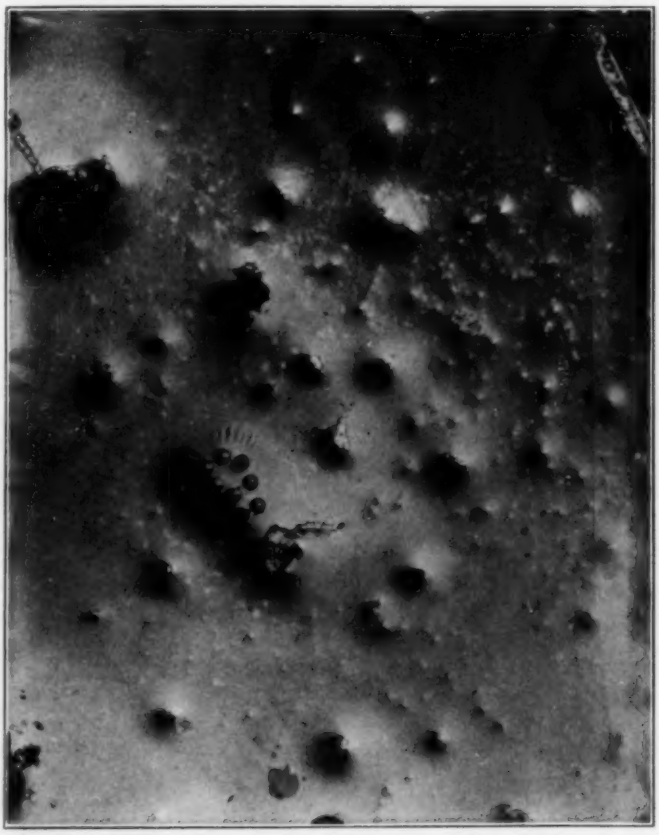

Fig. 10.—Atmospheric pollen plate showing prevalence of the common ragweed during the fall hay-fever season. × 125 diameters.

BUOYANCY OF THE RAGWEED POLLENS

Our pollenometric records demonstrated the remarkable buoyancy of the common ragweed pollen. In the vicinity of New Orleans, the common ragweed (*Ambrosia elatior*) is not found, being replaced by the giant ragweed (*Ambrosia trifida*), the nearest being about 5 miles from the station from which the important pollen records were made.

Nevertheless, during the prevalence of a 20-mile wind, the common rag-weed pollen grains were freely deposited on the plates located on the eighth floor of the Audubon Office Building of New Orleans.

On the other hand, the atmospheric pollen plates exposed at our Hendersonville (North Carolina) station (altitude 2,350 feet), Sept. 20, 1916, after the pollination of the common ragweed (*Ambrosia elatior*) had been ended in that section by the cold weather, gave negative

Fig. 11.—Pollen of corn. Its large size limits its potential area. This specimen is infected with the mycellium fungus to which the pollen of the *Gramineae* are susceptible. × 500 diameters.

results and hay-fever entirely disappeared, although at a distance of 15 miles the ragweeds were still pollinating profusely, with the usual number of hay-fever cases. While it has not yet been established to what distance the pollen grains of the common ragweed can be carried in sufficient numbers to cause hay-fever, our records for the past ten years show that it will not traverse this distance.

POTENTIAL AREA OF HAY-FEVER POLLENS

As already stated, only the plants with wind-borne pollen need be considered etiologically in hay-fever, and of these, only those which have been shown to give the hay-fever reaction. The distance, however, at which the wind-borne pollens, giving a positive reaction, are responsible for hay-fever is influenced by their buoyancy, which controls the potential area of these pollens.

The buoyancy of pollens varies principally according to the size of the grains, this being also influenced by their external shape. The size of the hay-fever pollen grains varies within considerable limits, among the smallest being the common ragweed (Fig. 7), measuring 15 microns in diameter, and among the largest the pollen of the corn (80 microns, Fig. 11).

As the potential area is an important subject in the consideration of hay-fever, we have prepared a table by which this area for pollens of 10 to 100 microns in diameter, and with winds from 2 to 30 miles per hour, may be calculated.

CONVECTION OF HAY-FEVER POLLENS[7]

Any small particles which appear to float in the air, like a cloud of dust, fog, pollen, etc., are really going through a process of falling with a uniform velocity. The rate of falling is under these conditions independent of the density of the particle. If the surface of the particle is rough the velocity is less than if it is smooth.

If the particles have the form of smooth spheres of a diameter not less than 0.001 mm., it has been shown both on theory and by actual experiment that the velocity with which such spheres fall is given by the formula:

$$v = \frac{2\,g\,r^2}{9\quad k} \quad \text{(Stokes' Law)}$$

where v = the velocity in centimeters per second, g = 980 cm. the acceleration of gravity, r = the radius of the sphere and k = the coefficient of viscosity for air = 0.00018.

By substituting the different values for the radius of spheres and the known constants in the above formula, the velocity for pollen grains of any size can be calculated. The calculation gives exact values for the smooth pollen grains only. The values will be considerably higher in the case of the pollen with spicules, the velocity being considerably less than the calculated value.

When the velocity has been calculated, the time of fall of a pollen grain can be calculated for any distance by dividing the distance by the

7. Report by Prof. J. H. Clo, Department of Physics, Tulane University, New Orleans, and C. C. Clark, Acting Chief of Weather Bureau, Washington, D. C.

velocity. If a wind is carrying the pollen horizontally while it is thus falling, the distance it will be carried is equal to the product of the velocity of the wind times the time of fall. In this way the distance which grains of different size will be carried can be calculated.

The above formula has been used extensively in physical investigations, and there are numerous proofs of its correctness. The accepted value of the electric charge of an electron or cathode particle depends on the accuracy of this formula.

Table 1 shows the distances that pollen grains of various diameters will be carried by different winds from plants of different heights.

TABLE 1.—POTENTIAL RADII OF HAY-FEVER PLANTS

Table of distances traversed by pollens of various sizes

Diameter in Microns	Velocity of Fall, Ft. Sec.	Distances in Feet Traversed by Pollen Blown from Plant 2½ Feet High Along Level Ground with Wind Velocity of							Distances in Feet Traversed by Pollen Blown from Plant 5 Feet High Along Level Ground with Wind Velocity of						
		2 Mi. Hr.	5 Mi. Hr.	10 Mi. Hr.	15 Mi. Hr.	20 Mi. Hr.	25 Mi. Hr.	30 Mi. Hr.	2 Mi. Hr.	5 Mi. Hr.	10 Mi. Hr.	15 Mi. Hr.	20 Mi. Hr.	25 Mi. Hr.	30 Mi. Hr.
10	0.04	184.0	460.0	920	1,380.0	1,840	2,300.0	½ mi. 2,760	368	920	1,840	2,760	3,680	4,600	1 mi. 5,520
15	0.09	82.0	205.0	410	615.0	820	1,025.0	1,230	164	410	⅛ mi. 820	1,230	⅛ mi. 1,640	2,000	0.45 mi. 2,460
20	0.16	46.0	115.0	230	345.0	460	575.0	690	92	230	460	690	920	1,150	1,380
30	0.36	20.0	51.0	102	153.0	204	255.0	306	40	102	204	306	408	510	602
40	0.64	11.0	28.5	57	85.5	114	142.5	171	22	57	114	171	228	285	342
50	1.00	7.5	18.5	37	55.5	74	92.5	111	15	37	74	111	148	185	222
60	1.44	5.0	12.5	25	37.5	51	62.5	76	10	25	50	75	102	127	132
70	1.96	4.0	10.0	19	29.0	38	50.0	58	8	19	38	57	77	96	116
80	2.56	3.0	7.0	14	21.0	28	35.0	43	6	14	28	42	56	70	86
90	3.24	2.0	5.5	11	16.5	22	27.5	33	4	11	22	33	44	55	66
100	4.00	2.0	5.0	9	14.0	18	25.0	27	4	9	18	27	36	45	54

NOTE.—For spiculated pollens, add 10 to 50 per cent., according to their size and the length of the spicules.

While Table 1 is correct for distances on level ground and under a steady wind of the given velocity, these exact conditions are not often met with. Such obstructions as houses, trees and shrubbery, will deflect the wind and cause the currents of air to go upward instead of horizontally. Hilly land also causes considerable variation in the effects of the wind, and also the vertical currents in summer. In spite of this, however, we have found this table of practical value as corroborated by our pollenometric records. It is especially useful in determining the relative distances traversed by various pollens. The common ragweed (*Ambrosia elatior*), for instance, having grains measuring 15 microns in diameter and spiculated, will traverse one-half mile in a wind of 20 miles per hour on level ground, and many times this dis-

tance when deflected by upward currents, while the smooth corn pollen will travel only 102 feet under the same conditions. Under similar conditions, the pollen grains of the grasses (*Gramineae*), which usually measure about 40 microns in diameter, will traverse 456 feet.

These calculations compare favorably with the records of our pollenometric records. The common rag-weed (*Ambrosia elatior*, with grains measuring 15 microns in diameter) will travel the greatest distance, which easily gives it the preponderance of hay-fever cases in the localities in which it is found.

The small number of cases of corn pollen hay-fever compared with that of grass pollen hay-fever is explained principally by the difference of size, causing a contracted radius of infection. In addition to this, corn is not found as a weed in the cities and suburbs, as we find the grasses and ragweeds, which, together with the limited carrying distance, explains the comparative rarity of corn pollen hay-fever.

NUMERICAL DISTRIBUTION OF HAY-FEVER POLLENS

In addition to the convection of pollen by the wind, we must consider the numerical distribution of these pollens. This is not subject to any special rule, as for the distance, and we must be guided by the pollenometric records as a basis of calculation.

These records show that this distribution is approximately inversely as the square of the distance. Theoretically, if the ground were level and the wind steady and from one direction, the distribution of the pollen would be inversely as the distance. On land, with its shrubbery, trees and buildings, the wind becomes a succession of wind currents, so that at one time the wind is at its full velocity, and at another may be almost still. During this interval, the pollen falls with a velocity shown in the table, and in this way a large portion is deposited on its way to the terminal distance based on the wind velocity. There are certain variations in the direction of the winds also, causing the pollen to be distributed in various directions. While, therefore, there is no exact rule for calculating the numerical distribution of the pollen, the rate established by our pollenometric records is approximately correct.

Some investigators have endeavored to calculate the amount of pollen generated by the ragweeds, and have estimated from this the amount of pollen in the atmosphere. As a matter of careful observation, however, over 50 per cent. of the pollen falls within the immediate neighborhood of these weeds. This is shown by the fact that when they grow in great abundance, the ground under them is colored yellow by the fallen pollen, this color rapidly diminishing a few yards from the plants. While, therefore, these pollens are distributed in great

numbers, the quantity in the air is really only a small proportion of the pollen generated.

The buoyancy of the common ragweed pollen can be better appreciated when it is stated that it requires 380,000,000 pollen grains to make 1 gm.

AMOUNT OF POLLEN DISTRIBUTED BY HAY-FEVER WEEDS

In order to ascertain the number of pollen distributed by hay-fever weeds, the following test was made June 24, 1916:

Six of the flowers of the bastard feverfew (*Parthenium hysterophorus*) while attached to the parent plant were enclosed in a small case, one end being left open to prevent the accumulation of moisture. At the end of four days the floor of the receptacle was found to be dusted with the pollen. To facilitate the counting, this area was divided into 110 squares and the pollen of one of the squares placed under the microscope. This gave a count of approximately 5,000 pollen grains for each square. As there were 110 squares, this showed that there were 550,000 pollen grains in the receptacle. Dividing this by 4 gave the number of pollen grains distributed by one flower in one day, this being 22,916.

An average large bush (3 feet, 10 inches in height) of the parthenium was then selected and the flowers counted, this being done by cutting off each flower. This count gave 9,902 flowers to the bush. Multiplying this by the number of pollen grains distributed by each flower, showed that the parthenium generates approximately 227,000,000 pollen grains per day.

The ragweeds, however, are much more prolific in their pollens, as shown in the following test: Aug. 23, 1916, a plant of the giant ragweed (*Ambrosia trifida*) was placed in such a position in the biological laboratory that all the pollen fell on the platform on which the plant was placed. The pollen which fell from 8 a. m. to 1 p. m. was divided into spaces and the pollen of one of these placed under the microscope and the grains counted. The total number calculated from these was found to be approximately 8,000,000,000. In this case there were only about thirty racemes pollinating, which is only a small number for this weed.

Similar experiments demonstrated that the number of pollen grains generated in a field of grasses (*Paspalum dilatum*) during the active stage of pollination was about eight millions per square foot of surface. On account of the short distance from the ground (18 inches) and the large size of the grains (40 microns), only a small proportion of this pollen is carried into the air except during winds of high velocities (20 or more miles per hour).

An interesting point in connection with atmospheric pollen was demonstrated by these plates. A number of published reports show that atmospheric pollen came from the direction of the sea in which the nearest land was 200 miles, and it was, therefore, concluded that the pollen had traversed this great distance.

In New Orleans the ragweed area is northeast to northwest of the city, and under ordinary circumstances the pollen comes from this direction. Sept. 29, 1916, when the pollination of the ragweed was at its height in this locality, the wind, which was from the northeast, rose to 22 miles per hour and the pollen count reached 114. Two days afterward, the wind veered to the southeast, in which direction but little ragweed is found. The pollen plates, however, continued to show nineteen pollen grains for two days afterwards. This shows that the high wind had infected the atmosphere with the ragweed pollen for so many miles and to such an altitude, that for several days it continued to descend from the direction in which it had been carried. Had the initial record of the northeast wind not been made, it would have been supposed that the pollen had originated from some southern point of great distance.

WINDS IN RELATION TO HAY-FEVER

It is well known that hay-fever patients improve during a rain of several days' duration, and that their symptoms become aggravated during the prevalence of high winds. The former is due to the fact that pollens floating in the atmosphere are precipitated by the rain and that no more pollen rises until it ceases. This has been clearly shown by our pollenometric records. During high winds, on the other hand, not only are more pollen grains shaken from the plants, but the liberated grains are carried to proportionately greater distances.

These records also demonstrate that there is a definite relation between the wind velocities and the amount of pollen in the air, the clinical reports proving that there is a similar relation between the resulting pollen in the air and the symptoms of hay-fever subjects.

Table 2, which is a partial report of one of our stations, shows the records of the atmospheric pollen plates in relation to the daily maximum and mean wind velocities and directions, the estimated number of pollen grains per cubic yard of air, and the mean temperatures and the rainfall. As this station is at an elevation of 100 feet (eighth floor of office building) and at least 2 miles from any large weed areas, the records are uninfluenced by any special local conditions. The table gives the number of grass pollens, of ambrosia pollens (common and giant ragweed) and of "other pollens," the latter including the docks, amaranths, chenopods, marsh elders and cockleburs, all of which give a positive reaction for hay-fever, but are in this locality of minor importance.

TABLE 2.—Hay-Fever Pollens in Relation to Wind, Temperature and Rain

	Grass Pollens	Ambrosia Pollens	Other Pollens	Number of Pollens Per Square Yard of Air	Maximum Wind	Mean Wind	Direction	Mean Temperature	Rain
1916									
9/22	4	5	2	29	10	3.8	N.W. S.	78	0.0
9/23	..	7	..	22	14	5.4	S. S.E.	80	0.0
9/26	1	9	..	31	16	6.0	S. S.E.	80	0.01
9/28	..	15	..	48	15	4.3	S. N.E.	82	0.02
9/29	..	114	..	305	22	13.4	N.E.	68	0.0
10/ 1	..	36	..	115	16	7.5	N.E. E.	68	0.0
10/ 2	..	19	..	61	14	7.4	S.E. E.	71	0.0
10/ 3	..	6	..	19	12	5.9	E.	72	0.0
10/ 4	..	7	..	22	12	6.2	N.E. E.	74	0.0
10/ 5	..	11	..	35	21	10.7	N.E.	73	0.01
10/ 6	2	6	2	29	16	7.2	N.E. E.	78	0.01
10/ 7	1	7	..	26	17	7.9	E. N.E.	76	0.02
10/ 8	..	2	..	6	12	4.3	N. S.E.	80	1.85
10/ 9	..	8	..	26	7	2.9	N.W. S.	80	0.0
10/10	..	12	1	42	18	9.6	N.E.	74	0.0
10/11	..	11	..	35	18	7.7	N.E.	73	0.0
10/13	..	3	1	13	7	4.3	E. S.E.	77	0.0
10/14	..	9	2	35	10	5.0	S.E. S.	78	0.0
10/17	..	..	..	0	25	14.0	E.	72	2.58
10/18	..	1	4	16	24	11.5	N.E. S.W.	74	0.19
10/19	..	23	5	90	15	7.9	N.E. S.W.	76	0.0
10/20	..	5	5	32	23	13.4	N.W.	62	0.0
10/21	..	12	2	45	15	8.5	N.W.	58	0.0
10/24	..	..	2	6	8	4.2	E.	67	0.0
10/25	..	1	1	6	15	7.1	N.W.	70	0.0
10/26	..	8	2	32	17	10.1	N.E.	62	0.0
10/27	..	1	3	13	15	8.5	N.E.	66	0.0
10/28	..	1	8	29	12	6.5	N.E. E.	67	0.0
10/29	..	..	1	3	9	4.5	N.W. N.	70	0.0
10/31	..	..	2	6	8	3.7	N.W.	72	0.0

Our clinical records show that the most severe symptoms of fall hay-fever were on September 29, 30, 31 and October 1, which corresponds with the high wave of the recorded pollen count.

After the nostrils have become irritated by a large number of pollen grains they become sensitive to a smaller number than under ordinary conditions. Thus, each period of aggravated hay-fever was followed by symptoms in excess of the record of the pollen counts.

As will be noted, these counts are influenced not only by the wind velocity, but also by its direction, this being regulated by the locality of the nearest large weed areas. September 22, there were 11 pollen grains per square centimeter with a wind of 10 miles from the northwest, while on September 25 there were only 7 with a wind of 14 miles from the southeast.

Towards the latter part of October the pollination of the ragweed was reaching its limit, which explains the irregular count after October 15. October 29, the ragweed pollens were no longer recorded on our plates, and our clinical records show that the fall hay-fever season has passed.

The effect of rain on the pollen was also clearly indicated. October 17, the rain of 2.58 inches caused the ragweed pollen to disappear from the plates during that day, and also the following (1 per sq. cm.) in spite of the fact that the wind had reached a velocity of twenty-four miles per hours and was from a northerly direction. Local showers have little effect, as shown on September 26 and 28, and October 5, 6 and 7.

INFLUENCE OF TEMPERATURE

It has been frequently reported that hay-fever is aggravated by hot weather, but the records for the past year indicate that high temperatures have no special effect. On the contrary, the records both pollenometric and clinical show that most of the severe stages of hay-fever developed on days when the temperature was unusually low for the season. Thus, the most severe stage of hay-fever during the past season in New Orleans was on September 29 and 30, when the mean daily temperature was 68, the normal for this being about 80. The lower temperature, however, was only incidental, being due to the high wind (22 miles per hour) which blew from the northeast, which in this case was also from the direction of the hay-fever area.

EFFECTS OF PREVENTIVE MEASURES AGAINST HAY-FEVER POLLENS

Our pollenometric records during the past year demonstrate that the vernal type of hay-fever is due principally to the pollen of the grasses, and that these are not carried a long distance by the wind. In neighborhoods in which the weeds are systematically cut, the pollen count is very low and the cases of hay-fever unusual. In other localities, in which the weeds have been neglected, the pollen count is high and cases of hay-fever common.

These records have also demonstrated very clearly that the vernal form of hay-fever may be practically eradicated by the enforcement of adequate grassweeds ordinances. In New Orleans, where, through the efforts of the local committee of the American Hay-Fever-Prevention

Association, cooperating with the Department of Public Property and the Board of Health, the grassweeds ordinance has been thoroughly enforced, vernal hay-fever has almost disappeared.

In the fall type of hay-fever, however, the results have not been so marked. The buoyancy of the pollen of the common ragweed (*Ambrosia elatior*) is such that it will travel several miles in winds of high velocity (15 to 20 miles per hour). In view of this, municipal efforts alone will not be able to eradicate fall hay-fever, although much benefit may be obtained. Complete relief will follow only when the public realizes the great benefit which will result from the eradication of the worthless ragweed that forms the principal cause, and state legislation reinforces municipal efforts in its eradication.

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THE SYSTOLIC BLOOD PRESSURE FOLLOWING EXERCISE; WITH REMARKS ON CARDIAC CAPACITY *

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The observations related in this article were undertaken after reading the recent articles published in this journal by Barringer[1] in which he describes a method used by him to estimate the capacity of the heart in normal and diseased subjects. The work has been done at the Hampstead Military Hospital, London, which institution has been set aside by the British War Office for the investigation and treatment of soldiers suffering from cardiac disabilities. After reading Barringer's article it seemed probable that we might find some qualitative difference between the blood pressure reaction following given test exercises, in healthy subjects and in those patients who form the greatest part of our material, namely, soldiers who suffer from the condition described as "irritable heart"; and that if such a difference could be discovered it would form a valuable help in sorting our patients for treatment. We have completed this comparison and have been unable to find the qualitative difference for which we looked, but in completing it we have acquired knowledge of the blood pressure reaction, which, so it seems to us, is at variance with the conclusions of Barringer. At present we publish such of our results as are relevant to a discussion of Barringer's hypothesis; confining the observations to the normal curve of systolic blood pressure which follows immediately on a complete test exercise.

Barringer's Test.—The subject performs a given amount of exercise. In some cases this is done by means of a Zuntz ergometer, in others by raising 5- or 10-pound dumb-bells from the shoulders, in others where larger amounts of work in a short space of time are

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1. Barringer, T. B., Jr., and Teschner, J.: The Treatment of Cardiac Insufficiency by a New Method of Dumb-Bells and Bars. The Circulatory Reaction to Exercise as a Test of the Heart's Functional Capacity. THE ARCHIVES INT. MED., 1915, **16,** 795. Barringer, T. B. Jr.; The Circulatory Reaction to Graduated Work as a Test of the Heart's Functional Capacity, Ibid., 1916, **17,** 363; Studies of the Heart's Functional Capacity as Estimated by the Circulatory Reaction to Graduated Work, Ibid., 1916, **17,** 670.

required, by swinging dumb-bells or a 25-pound bar from the floor above the head and back again. The time consumed in each form of exercise varies between thirty and 120 seconds.

For purposes of illustration we shall confine ourselves to the third form of exercise used by Barringer. His readings were taken at intervals with a Riva-Rocci manometer by the auscultatory method. We gather from his description that the first reading was obtained thirty seconds or less after the cessation of exercise. The actual moment is not stated, but the readings as charted, are placed on this time line. Succeeding readings were taken at one-minute (in some cases half-minute) intervals after the first. According to Barringer the first reading is higher than the second, indicating an initial fall of blood pressure, in healthy subjects who have undertaken moderate amounts of work. But in normal people after a full effort the second reading is the higher, indicating an initial rise of blood pressure which he names the "delayed rise." The occurrence of this rise is an index, according to this writer, that the full "cardiac capacity" has been reached, and the amount of work required to produce it is taken, both in normal and also in diseased subjects, as a measure of the functional capacity of the heart. We are led to understand that when the heart is submitted to a given amount of work, a qualitative difference appears in the succeeding curve of blood pressure; and it is to be emphasized that it is in that portion of the curve which is described during the first minute, or at the most the first minute and a half, of rest after exercise that this change is manifested; a change which is taken to indicate a "functional insufficiency" for the particular amount of work accomplished. The amount of work necessary to produce such insufficiency varies with the capacity of the heart, and is far greater in the normal subject than in those in whom the muscle is weakened by disease. Somewhat similar observations have been made by Gräupner,[2] whose work prompted that of Barringer; but Gräupner's first readings suffer from a similar defect to those of Barringer, in that their precise relation to exercise in point of time is not known; apparently it was not estimated.

From his experiments, Gräupner draws certain conclusions, namely:

1. Moderate amounts of work in strong persons produces, generally speaking, no changes in blood pressure (systolic) after work.

2. An increase in the work done results in the blood pressure standing higher immediately after work, then more or less quickly returning to normal.

3. If the work done is still more increased, we find a sinking of blood pressure immediately after the exercise. However, the blood pressure quickly rises above normal and then falls back to normal . . . As long as this secondary rise above

2. Graüpner: Deutsch. med. Wchnschr., 1906, No. 26. Graüpner and Siegel: Ztschr. f. exper. Path. u. Therap., 1906, **3**, 109.

normal is present "functional insufficiency" exists . . . The weaker the myocardium, the less the amount of work necessary to produce "functional insufficiency."

4. If primary myocardial weakness is present, we speak of "pathological insufficiency." This is characterized by primary sinking of the blood pressure below normal, gradually rising to normal.

Method.—In the early experiments which we instituted, the conditions approximated as closely as possible to those described in Barringer's papers. We soon found that only rarely could the first readings be obtained earlier than twenty to twenty-five seconds after the cessation of work. On one occasion, however, after a subject had performed a small amount of work which there was no clinical reason to believe approached the limits of his capacity, and following which he showed no signs of distress, a reading was obtained within fifteen seconds. This reading was followed, as shown in successive readings, by a rise in systolic pressure.

This seemed to indicate the advisability of using a method which would enable us to obtain constant early readings.

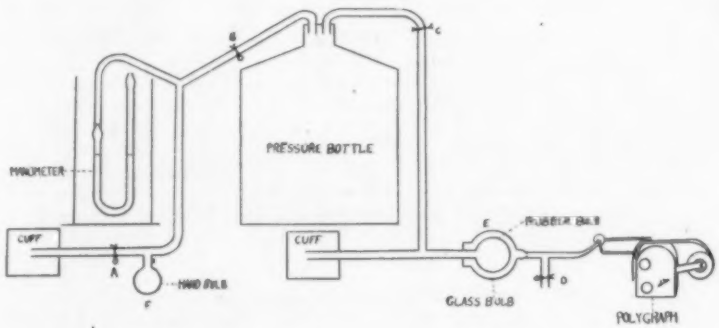

Fig. 1.—Apparatus used in Author's experiments, more fully described in the text.

A large bottle is connected (Fig. 1) by means of one system of rubber tubing with an arm cuff and a mercury manometer, so that when cock A is open and cock B closed this portion is an ordinary Riva-Rocci instrument. By means of the other system of tubing the bottle is connected with a cuff lying on the other arm, and through the bulb E (a rubber bulb open at the proximal end, inside of a glass bulb open at the distal end, such as is used in the Erlanger sphygmomanometer) to the writing lever of a Mackenzie ink polygraph.

Before the exercise the pressure bottle is filled with air at the desired pressure by the hand bulb (F) after closing cocks A and C and opening cock B. The amount of pressure used is such as has been shown in the given case to release into the two cuffs a pressure slightly below the subject's normal systolic pressure. Cocks B and C are closed, and cocks A and D opened. The subject then does a definite amount of work. Immediately before the cessation of work cocks B and C are opened, releasing the desired pressure into each cuff. The subject sits down at the end of exercise, cock D is immediately closed and the pulse at once recorded by the polygraph.

When the subject resumes the sitting posture, the cuff on the other arm, that is, that used for blood pressure determination, is already filled at a convenient pressure and only one or more pumps of the hand bulb are necessary to raise it above systolic pressure and to obliterate the pulse. By using this simple device we obtain (1) a continuous curve of pulse rate almost from the instant exercise ceases—these pulse rates will not be discussed in the present communication—and (2) a reading of systolic pressure, always within ten seconds, often within four or five seconds of the termination of exercise. This reading and the following readings are written on the pulse curve and their time relations subsequently determined accurately. As soon as the first pulse beats have forced the armlet the cuff pressure is raised a few millimeters until the beats again force their way through, and so the pressure curve is followed for from one-half to one minute by readings taken in rapid succession (at about five-second intervals) until a maximal point is reached; the cuff pressure is then released, and the remaining readings are taken more leisurely, the cuff pressure being reduced between each.

Barringer has used the auscultatory method of taking blood pressures, and criticizes the palpatory method. Both are, indeed, subjective methods, and facility in the use of either is a matter of practice. The supposed greater accuracy of the auscultatory method is unproved. Assuming a difference to exist, it is very slight; we have rarely found it to be more than 2 to 4 millimeters. The great advantage of the palpatory method is its quickness in obtaining early readings. We eliminate error so far as possible by repeating each observation

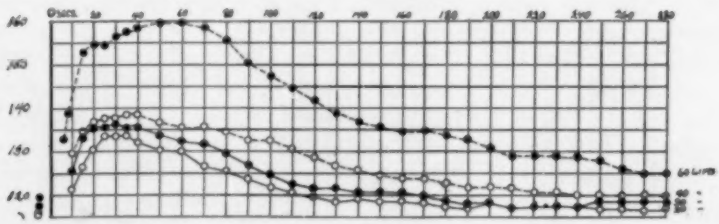

Fig. 2.—Weight of subject, 140 pounds; lift, two 10-pound dumbbells through 6 feet; time, 1 lift in 2 seconds. With 30 lifts, slight breathlessness; with 40 lifts, moderate breathlessness; with 60 lifts, considerable breathlessness and slight distress. As in all curves, the zero mark represents the cessation of exercise, the readings charted to the left of this line being controls taken before exercise.

on three successive days, plotting all three curves and taking the average of the three. The curves here published are averages of this kind.

We cannot agree that the continuous pressure of the cuff for a minute or less on the arm influences the readings in any appreciable degree. Before each observation the subject rests until constant and normal blood pressures and pulse rate are reached; these control observations are taken in the same fashion as those above described and the effect of cuff pressure on blood pressure thereby eliminated. The average of the three sets of control readings is given in conjunction with each curve published.

The exercises used are the swinging of two 10-pound dumbbells from the floor to above the head, the number of lifts varying from ten to sixty, the rate of lifting varying between 1 lift in 2, 1 lift in 3, and 1 lift in 4 seconds (guided by metronome). Not more than three different exercises are performed by the same subject in one day, and full rest is given between each. The possible influence of the effects of one exercise on another are eliminated

in this fashion and by varying the order of a given set of exercises on succeeding days.

The Blood Pressure Curve.—A young and healthy adult accomplishes 20 lifts at the rate of 1 lift in 2 seconds without breathlessness or subsequent fatigue; at the same rate he can accomplish 60 lifts more or less at the expense of some breathlessness and a varying amount of subsequent fatigue. But whether the

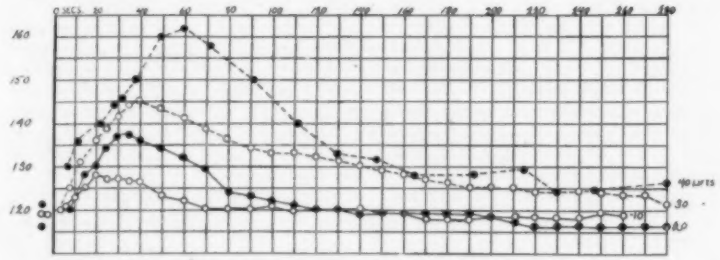

Fig. 3.—Weight of subject, 154 pounds; lift, two 10-pound dumbbells through 5 feet 10 inches; time 1 lift in 2 seconds. With 20 lifts, no breathlessness; with 30 lifts, moderate breathlessness and slight distress; with 40 lifts, considerable breathlessness and distress.

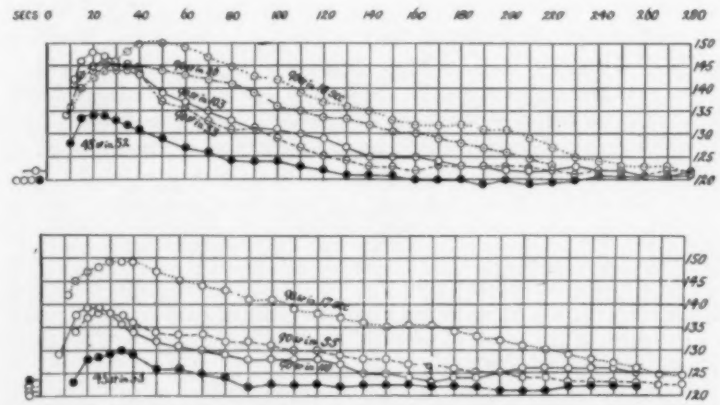

Fig. 4.—These two curves are the records of blood pressure following stairs climbing in normal subjects. The rate varied from a leisurely walk to a half run; the first producing in both cases practically no symptoms, the last resulting in considerable breathlessness, with gradations between the two. In the experiments, the results of which are figured in black, half as many stairs were climbed as in the other exercises. Each stair was 9 inches high.

lifts are 20, 30, 40, or 60, the reaction is qualitatively the same. The earliest readings show a prominent *rise* of blood pressure. An example of four reactions (each the average of three complete observations) is shown in Figure 2, and it may be taken as in most respects characteristic. The chart shows the after effects of 20, 30, 40, and 60 lifts (1 lift in 2 seconds) on the systolic blood

pressure. The control readings lie between 115 and 120 mm. Hg. The readings taken within the first ten seconds lie between 122 and 133 mm. Hg. From these points the curves sweep upward, reaching summits varying between 134 and 160 mm. Hg. Providing there is any reaction, *the rise is always present whatever the amount of work.* In this instance, as in most though not all instances, the greater the amount of work the higher is the first reading. In this, as in most instances, the amount of the rise varies directly with the amount of work.[3]

In the second chart (Fig. 3) the gradation is remarkably uniform.

Another feature which almost all these serial curves from normal subjects display, perfectly or in part, is the prolongation of the rise with increasing increments of work. The summit with different amounts of work is reached within 20 to 60 seconds; beyond 60 seconds we have not seen it prolonged. Beyond these points the curves fall gradually to the normal levels; they reach the normal line in times which vary with the amount of work; the fall is complete within 1½ or 2 minutes on the less severe exercises; and in 4 minutes, or perhaps a little longer, with the most severe exercises.

DISCUSSION

The conclusion which we draw from our observations is that as an immediate sequence of accomplished exercise, whether that exercise is moderate in degree, or whether it calls forth a full effort on the part of the person[4] who performs it, there is a rise of systolic blood pressure. The curve rises from a little above the original normal level to a point far above it; the rise is abrupt and has largely escaped detection on this account. This rise, in cases in which it is discovered, is spoken of by Barringer as the "delayed rise," and by him is considered to show that the exercise which produces it has overloaded the heart. With this conclusion we naturally disagree, but comprehend the manner in which he has been led to it. In most instances of moderate effort the whole of the rise to its summit will have been completed before Barringer obtains his first reading. In instances of great effort the rise will often be prolonged sufficiently for the first reading to be taken *on the rise;* the second reading will then be taken on the fall, or possibly on the continuation of the rise. In the first eventuality the difference in the readings will often be inconspicuous, that is, such few millimeters of mercury as are given in most of Barringer's tables;[5] in the second eventuality the rise will be conspicuous.

To speak of the rise ("delayed rise") itself as an index of a change in the circulatory reaction is, in the light of our experiences, unsound; to speak of a delay in the full development of the rise with severe effort, is usually to speak correctly. Even if it be admitted that this

3. Exceptions are found where two or more curves of such a series fall almost together.

4. We refer deliberately to the effort of the person and not to the effort of the heart, but we do not wish thereby to infer that the amount of work was limited by muscular fatigue.

5. The delayed rise as tabulated by Barringer is frequently no more than 2 mm. Hg, a difference which in our opinion is well within the error of measurement, however such readings are taken.

delay is of value, Barringer's method of determining it is too precarious to be serviceable. As the first reading is taken a little earlier or a little later, or as the second reading is taken a little later or a little earlier, so a fall becomes a rise, or a rise a fall. We regard this method of ascertaining *the shape of the blood pressure curve* to be without value, on account of the large variations in pressure which occur in the fraction of a minute following accomplished exercise.

But when we turn to the general thesis that such curves, even if *properly determined,* are indexes of the capacity of the heart, criticism is on broader lines. Briefly, we think that it is to be deplored that such theses are put forward in the present state of our knowledge. In so postulating a test of capacity Barringer does not stand alone, but in company with an increasing body of workers among whom little or no agreement of thought or methods is to be discovered.

THE USE OF THE PHRASES CARDIAC CAPACITY, CARDIAC EFFICIENCY

In speaking of a reservoir as capacious, an adjective is employed which in common parlance is convenient enough; but convenience renders the qualification no more exact. In dealing with matters practical, to state that a reservoir has a large capacity is insufficient; the statement of content is made in terms of the measure employed in gauging such capacity; the capacity is so many cubic feet, more or less. It is a truism that if the amount or size of a thing cannot be stated in terms of measure it cannot be stated at all; and however convenient it may be in conversation to refer to the size of a given object in general terms, such a device is frankly time and labor saving, or else it is deceptive.

It is common to see the phrase "capacity of the heart" employed, it is less common to see this phrase defined; but it may be presumed that it conveys the meaning "capacity to do work." Now the amount of work which can be done by an organ such as the heart, may or may not be measurable. If measurable in terms of foot-pounds per second, we are justified in speaking of cardiac capacity in this sense, adding the precise number of foot-pounds of work per second of which the heart is capable. If not measurable in these or some other units, the term cardiac capacity becomes a meaningless or misleading phrase. The work done by the heart in animal experiment and under given circumstances has been differently computed by various workers; such estimates are recognized as approximations subject to further revision. The work done by the heart in the intact and sentient animal at rest has never been accurately computed; still less has the *capacity* of the heart for work in circumstance of overload. It has become fashionable, nevertheless, to express the capacity of the heart for work in

terms of measure, terms which do not measure that capacity, but something which is quite different. Perhaps the pressure in millimeters of mercury necessary to collapse the brachial artery at a given moment and in a given condition of the body, or a series of such readings, is adopted. Perhaps similar readings of pulse rate are taken. The first is allowed as a measure by no means perfect of systolic blood pressure; the latter is allowed in most circumstances as a measure of ventricular rate. But they are no more than that. A curve of systolic blood pressure during or following exercise may be an exact expression of real events; but these events are blood pressure events and the measure is of blood pressure and not of cardiac work. It may prove that a certain form of blood pressure curve following a given exercise is found only in those who manifest grave signs of heart disease, and in whom the life history is to be short. We gain no advantage by concluding on anything but fully sufficient grounds that inefficiency or depressed cardiac capacity is responsible for the peculiarity of the curve on the one hand, the short life history on the other; we lose an advantage if thereby our vision of the real issue is clouded. The curve of blood pressure in question may be in our experience a sign that life is precarious, or that certain therapeutic measures may be adopted to the benefit of the subject. If this or that is the ascertained fact, it should suffice; it can be utilized to serve our ends just as satisfactorily without the interposition of hypothesis. The moment that the term "cardiac capacity" is introduced, though it may be introduced simply and solely to describe a given phenomenon of blood pressure or a series of such phenomena, additional conceptions of the heart as a whole or of the heart muscle in particular (histologic condition of the myocardium, reserve power of the muscle, etc.) are awakened, conceptions which as likely as not are unjustified, conceptions which in the minds of few workers will be identical.

When we are in the presence of physical signs and symptoms which unequivocally display slackening of the circulation, and when other physical signs point with equal clearness to *disease* of the heart as the central defect in the patient, then we may be justified in referring to cardiac inefficiency in summing up the condition; we *may* be justified also in conceiving a lowered cardiac capacity for work. Yet even in these circumstances we are often unable positively to assert that the heart is incapable of a normal amount of work; for though the circulation is failing, yet the heart may be overburdened with work (as a result of high peripheral resistance, extreme valvular obstruction, or the mechanical disadvantage of dilatation); and often, for aught we know, the work accomplished by a heart where circulatory failure is

manifest, is greater than the work to which a healthy organ could submit. The crux is that we have no measure of one or the other.

Admittedly the present argument applies with least force to such patients; but it is not in them that isolated physical signs are used as dependable; it is in the borderline case, or the case in which there are no other definite signs of circulatory failure, that they are employed, and employed, so it seems to us, often with insufficient justification.

A NEW INTERPRETATION OF THE PATHOLOGIC HISTOLOGY OF HODGKIN'S DISEASE*

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There are two outstanding theories concerning the nature and origin of Hodgkin's disease: one, that it is primarily an infective granulomatous lesion of the lymph nodes with secondary changes in the spleen, liver and other tissues; the second theory postulates that the disease is neoplasmic from the beginning. Neither offers an acceptable explanation of the process as a whole, and there is considerable evidence in contradiction of both.

The histologic changes in Hodgkin's disease were originally described by Sternberg[1] as the expression of a peculiar type of lymph node tuberculosis. Repeated efforts to detect tubercle bacilli in suitably stained microscopic preparations, and the injection of freshly emulsified lymph nodes into susceptible animals, have failed, however, to confirm this view, and it has since been generally abandoned. More recent efforts to implicate a diphtheroid micro-organism as the cause of Hodgkin's disease have likewise been discredited. Nevertheless, the prevalent opinion seems to be that the process is inflammatory, the neoplasmic theory having failed of popular acceptance largely because the histologic changes in the lymph nodes and elsewhere are more in consonance with the conception of a granuloma. As a matter of fact, Hodgkin's disease appears to me to exemplify the frequently neglected fact that inflammation and neoplasia share several important features in common, and that the distinction between the two is, at best, academic and artificial, and, at times, impossible. Thus, the histologic changes in Hodgkin's disease bear a resemblance to those of tuberculosis on the one hand, and to a malignant connective tissue tumor on the other, while the distribution of the lesions in the liver, kidney, bone marrow, and other tissues not commonly included in the lymphoid system, is strikingly like that of a metastasizing tumor, but is also explicable on the basis of inflammatory hyperplasia of pre-existing lymphomatous foci. There is still another possibility, however, which does not appear to have been previously emphasized, namely, that the histologic changes in the lymph nodes, spleen and other parts of the

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* From the Laboratories of Pathology, Bellevue and Allied Hospitals, Director: Dr. Charles Norris.

1. Sternberg: Centralbl. f. d. Grenzgeb. d. Med. u. Chir., 1899, 2, 641.

lymphoid apparatus in Hodgkin's disease constitute a systemic process with multiple foci of disease arising in different localities at approximately the same time and in response to the same provocative agent. In other words, the fully developed Hodgkin's disease, although possessing a histology all its own and maintaining in this regard an unmistakable individuality, nevertheless partakes of the nature of an infective granuloma on the one side, and of systemic lymphosarcomatosis on the other — that is to say, the disease is neither a pure granuloma nor a neoplasm, but a lesion belonging to a group for which a descriptive title has not yet been formulated, and which may, with propriety, be made to include, in addition, mycosis fungoides, Cohnheim's pseudoleukemia[2] and related conditions. The facts on which this opinion is based were derived largely from the microscopic study of forty-seven cases of Hodgkin's disease observed at the New York and Bellevue Hospitals, in seven of which postmortem investigation was permitted, and partly from anatomic and histologic observations carried out in conjunction with Dr. J. Frank Fraser[3] in seven cases of mycosis fungoides.

The first observable change in the lymph nodes in Hodgkin's disease consists in hyperplasia of lymphoid cells, with regeneration of the germinal follicles. This observation was made independently by Longcope,[4] Symmers[5] and Cunningham,[6] and is susceptible of substantiation by microscopic examination of the smaller nodules commonly to be found at the periphery of the massive enlargements in the neck, axilla and elsewhere. Incidentally, this histologic feature may constitute a source of error in the determination of the nature of the process, since the change in question is identical with that to be found in similar situations in tuberculous lymphadenitis, benign lymphoma, pseudoleukemia, and other conditions which are conceived in simple lymphoid hyperplasia and in which differentiation at the outset is consequently impossible. Similarly, the first observable histologic change in the spleen in Hodgkin's disease consists in hyperplasia of the lymphoid follicles of identical appearance with that seen in other splenic lesions, notably syphilis, tuberculosis, and status lymphaticus. Again, the first observable histologic change in the liver, kidney, bone marrow and other tissues in Hodgkin's disease consists in the appearance of minute lymphomatous foci indistinguishable from those encountered in the

2. Cohnheim: Virchows Arch. f. path. Anat., 1865, **33,** 451. Symmers, Douglas: The Archives Int. Med., 1909, **4,** 218. See Footnote 5.

3. To be published.

4. Longcope: Bull. Ayer Clin. Lab., 1903, **1,** 4.

5. Symmers, D.: Certain Unusual Lesions of the Lymphatic Apparatus, Including a Description of Primary Hodgkin's Disease of the Spleen and a Case of Gastro-Intestinal Pseudoleukemia, The Archives Int. Med., 1909, **4,** 218.

6. Cunningham: Am. Jour. Med. Sc., 1915, **101,** 868.

same situation in related diseases. In other words, the preliminary hyperplasia of lymphoid cells in Hodgkin's disease is not to be distinguished microscopically from that which occurs in the same locality in a half dozen other conditions, and it is only when histologic developments have trespassed beyond this point that differentiation becomes possible. As development proceeds, however, the hyperplastic lymph nodes in Hodgkin's disease begin to lose their architectural identity, the germinal follicles disappear, the lymph cords are merged into broad sheets of proliferating lymphoid cells, and at least two alien cells make their appearance and lend individuality to the microscopic picture. One of these cells is to be found in varying numbers lying free in the lymph sinuses. It is a large, rounded cell, indistinguishable from that frequently to be observed in other tissues, but bearing a striking resemblance to the nongranular, mononuclear cells of the normal bone marrow. The other is a much larger cell of identical morphology with that encountered in the normal bone marrow in the form of myeloplaxes. In the lymph nodes in the early stage of Hodgkin's disease these myeloid giant cells lie free among the lymphoid cells, and, in a later stage, may be seen as individual cells resting in the tissue spaces of a lymph node which has now become more or less richly permeated by delicate fibrous trabeculae. In the liver, spleen and other tissues affected by Hodgkin's disease the histologic changes are identical with those in the lymph nodes, or, at all events, there is no essential difference, and the microscopic diagnosis may be made with equal facility.

There is still another cell which forms an important feature of the pathologic histology of Hodgkin's disease, and which is found in varying numbers in a large percentage of all cases, namely, the polynuclear eosinophil. The significance of this cell in Hodgkin's disease, as elsewhere, is not altogether clear. There is an apparently closely related cell whose presence as part of the histologic change in Hodgkin's disease seems to have been overlooked, or whose identity has been confused with that of the eosinophil, namely, the eosinophilic myelocyte. It occurs in varying numbers in the lymph nodes in about a third of all cases. Sometimes it is the only eosinophilic cell present; at other times it is associated with the presence of polynuclear eosinophils, from which it is to be differentiated by the fact that it possesses but a single nucleus. Otherwise its appearance in the fixed tissues is identical. In a case of Hodgkin's disease which recently came under my notice, the lymph nodes presented vast hordes of eosinophilic myelocytes arranged in clumps of such size as to occupy a large part of the low power field of the microscope, and, in a second case, myelocytes were present in excessive numbers in the lymph nodes and visceral nodules, and in the blood as part of a terminal leukocytosis.

The detection of eosinophilic myelocytes in the lymph nodes is a further indication that Hodgkin's disease is associated with disturbances in the bone marrow, and their presence in that situation is reasonably to be ascribed to the fact that the marrow has not been able to supply eosinophils in adequate numbers, and has consequently been forced to disgorge a similarly granulated substitute.

In various forms of helminthiasis there is an eosinophilia in the blood varying between 5 per cent. and 85 per cent., and at the site of attachment of ankylostomata to the intestinal mucosa it is said that there is often a marked accumulation of eosinophils (Todd). It is assumed, therefore, that certain parasitic worms manufacture and inject into their host substances which are not only capable of stimulating the expulsion of eosinophils from the bone marrow, but which are also capable of attracting eosinophils toward the source of the stimulus. A similar explanation appears to be applicable to the appendix in certain subacute infective lesions attended by enormous infiltration of eosinophils. The fallopian tubes also offer a familiar example of localized infiltration of eosinophils. In this locality the process seems to bear a relationship to the subsiding stage of gonorrheal infection, and doubtless the chemotactic attraction is to be sought in the autolyzing pus so frequently associated with this variety of fallopian salpingitis.

The histologic alterations in the lymph nodes in Hodgkin's disease are aptly comparable to the so-called myeloid transformation of the hemopoietic viscera, notably the spleen and liver, in primary progressive pernicious anemia, and in certain sclerotic and hyperplastic lesions of the bone marrow. Thus, of seventeen cases of pernicious anemia, Gulland and Goodall[7] found myeloid foci in the liver in eight, and myelocytic infiltration of the spleen in four, while in still another case the spleen exhibited typical bone marrow giant cells. Donhauser[8] has recorded an example of splenomegaly associated with hyperplastic changes in the bone marrow in which the spleen was the seat of innumerable myeloid foci composed of large mononuclear, nongranular cells, giant cells, myelocytes and normoblasts, the histologic picture, with the nucleated red cells excluded, presenting such a striking resemblance to that of the spleen in Hodgkin's disease as to render differentiation a matter of extreme difficulty. In this connection it is interesting to note that the anemia of Hodgkin's disease seldom approaches the pernicious type, so that the bone marrow does not undergo megaloblastic changes, but retains its ability to produce mature cells in sufficient numbers to meet the customary demands, thus obviating the necessity for auxiliary foci of red cell hematogenesis.

7. Gulland and Goodall: Jour. Path. and Bacteriol., 1905, **10,** 125.
8. Donhauser: Bull. Ayer Clin. Lab., 1908, **5,** 46.

In Hodgkin's disease the bone marrow often presents profound structural alterations. In one group of cases there is overgrowth of connective tissue resulting in obliteration of the marrow cavity. This is apt to be limited to certain parts of the marrow system or even to a focal distribution in individual bones. In a second group, the bone marrow is the seat of histologic changes of essentially the same character as those encountered in the lymph nodes and elsewhere. Finally, there is a third group of cases attended by extraordinary hyperplastic changes in the cells of the bone marrow, the increase affecting principally the myelocytes and the large nongranular cells of the lymphocytic type. Normoblasts may be present in increased numbers, but megaloblasts have never been described in any of the reports with which I am familiar, nor have I ever found them in any of the preparations that I have examined. The bone marrow giant cells are not increased, and may even be conspicuous by their diminished numbers — a fact which finds ready explanation in the occurrence of myeloid giant cells in such large numbers in the tissues beyond the osseous system as to impoverish the supply in the marrow, where, at best, giant cells are by no means numerous.

In short, the changes in the marrow in Hodgkin's disease are such as to provide a perfectly clear and logical explanation for the alterations in the extramedullary hemopoietic system and in such other viscera as may be involved. Whether the changes in the marrow are primary or not has no essential bearing. The fact remains that the presence of myeloid giant cells, eosinophils and eosinophilic myelocytes in the lymph nodes and elsewhere is an indication of disturbances in the bone marrow resulting in increased expulsion of these cells and their deposition in remote tissues. The only other possible explanation is that the myeloid changes in the hemapoietic viscera are reversionary — that the hemopoietic function of the lymph nodes, liver and spleen has been re-awakened, the occurrence of myeloid foci in them representing the structural expression of their rejuvenation. This explanation is, however, inapplicable to the organs beyond the hemopoietic system, namely, the kidney, suprarenal, lung, thyroid, etc., in all of which Hodgkin's disease sometimes initiates histologic changes similar to those in the lymph nodes and elsewhere. It is true that the human fetal spleen normally contains cells of the bone marrow type in the form of giant cells and myelocytes, all of which diminish and disappear as development proceeds. In the spleen of certain other mammals, however, myeloid foci persist throughout life. It is quite possible, therefore, that the human spleen may revert to the hematogenetic function of embryonal life, and the same is true of the liver; but as far as the lymph nodes are concerned, the explanation is

decidedly strained, since the embryonal lymph node is not an auxiliary of the marrow system, functionally or otherwise, and certainly the fully developed lymph node is not apt to assume a duty so remote from its own as to include the manufacture of alien cells. The conclusion, it seems to me, is inevitable, that the presence of myeloid giant cells and eosinophilic myelocytes in the lymph nodes and elsewhere in Hodgkin's disease is made possible only by the process of embolism from the bone marrow. Moreover, this explanation is strictly comparable to the discharge of normoblasts into the circulation after severe hemorrhage, to the occasional presence of myeloid giant cells in the capillaries of the liver and lungs, and to the enormous influx of giant cells and myelocytes into the spleen of certain lower animals following infection by the bacillus of hog cholera, pyocyaneus, anthrax and other microorganisms, and after repeated artificial hemorrhages.[9] In short, the interpretation in question is supported by both precedent and principle.

In a certain number of all cases of Hodgkin's disease necroses are present in the affected tissues, and the irregular type of temperature so frequently to be observed in the living patient is probably due to absorption of the products of necrosis, plus those derived from the more deliberate disintegration of cells. Whether the same explanation applies to the chronic relapsing fever described by Murchison,[10] Pel,[11] Ebstein[12] and others, is yet to be seen. The fact remains, however, that this type of fever is always associated with the presence of enormous numbers of focal necroses in the tissues involved, particularly the spleen. This explanation of the temperature disturbances in Hodgkin's disease is analogous to that usually offered for the fever so commonly observed in patients suffering from hypernephroma, in which variety of neoplasm necrotic and degenerative changes are almost constant. The contention likewise finds confirmation in the negative evidence offered by the lymphoid tissues in lymphosarcomatosis, where necroses are uncommon and disturbances of temperature are correspondingly infrequent.

Finally, the theory above outlined does not attempt to explain why a particular group of lymph nodes should become affected in Hodgkin's disease and apparently remain alone involved for months or years. The same general problem arises in connection with the occurrence and distribution of metastases in malignant growths, and seems, at the present moment, to be beyond the field of the explicable, unless, of course, it is regarded as another expression of chemotaxis. For

9. Pugliese: Fortschr. d. Med., 1897, **15,** 727. Opie: Am. Jour. Med. Sc., 1904, **127,** 988.
10. Murchison: Tr. Path. Soc., London, 1871, **21,** 372.
11. Pel: Berl. klin. Wchnschr., 1887, **24,** 644.
12. Ebstein: Berl. klin. Wchnschr., 1885, **22,** 565 and 837.

example, there is no apparent reason why certain tumors of the thyroid, prostate, breast, adrenal, etc., should give rise to secondary deposits in the bone marrow with such appalling freedom, nor, conversely, is it possible satisfactorily to explain the relative immunity of the spleen to metastatic growth, nor the almost complete immunity of the prostate to syphilis, and of the pancreas to tuberculosis. It is nevertheless true that, in Hodgkin's disease, a group of lymph nodes may become enlarged and remain for an almost indefinite period as the sole objective manifestation of a systemic process.

SUMMARY

Hodgkin's disease is primarily neither an infective nor a neoplasmic lesion of the lymph nodes, but a systemic disease which expresses a predilection for lymphoid tissues, giving rise to multiple foci of growth at approximately the same time and in response to the same provocative agent. The provocative agent, whatever its nature and origin may be, causes preliminary hyperplastic changes in the lymphoid tissues and initiates disturbances in the bone marrow, characterized, among other things, by proliferation of the nongranular mononuclear cells of the lymphocytic type, eosinophils and eosinophilic myelocytes. These cells, together with the myeloplaxes, are thrown into the circulation and filtered out by the lymph nodes or deposited in them in response to chemotactic attractions, the fibrotic changes in the recipient tissue representing a purely local reactive process. The histologic changes beyond the lymphoid system proper, namely, in the liver, kidneys, etc., represent a reaction on the part of normally existing lymphomatous foci to the same toxic substance which is responsible for the disturbances in the bone marrow and for the myeloid transformation of the lymph nodes.

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THE TREATMENT OF SYPHILIS OF THE CENTRAL NERVOUS SYSTEM

A COMPARISON OF MERCURIALIZED SERUM AND SALVARSANIZED SERUM *

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Cases of syphilis with positive findings in the spinal fluid treated during a period of three years following the opening of the Peter Bent Brigham Hospital may be divided into three groups. The patients of one group were treated with salvarsan, mercury and potassium iodid for a sufficiently long time to determine whether or not clinical and laboratory improvement would follow. If there was definite improvement, no change was made in the therapy. If improvement did not follow after a reasonable length of time, they were shifted into a second group the members of which received in addition to the above, salvarsanized serum intraspinally. In a third group were placed those patients having negative blood Wassermann reactions, and to them salvarsanized serum alone was given. Seventy-five patients were treated under this plan, and to them 450 intraspinal injections of salvarsanized serum were given in addition to the intravenous salvarsan and other medication. A detailed report of this work has appeared in a recent publication.[1]

At the end of this time, having satisfied ourselves concerning the relative efficiency of these different modes of treatment and the results to be derived from each, we decided to discontinue the use of salvarsanized serum and to substitute for it mercurialized serum prepared by the method suggested by Byrnes.[2] The very obvious advantages of the mercurialized serum are, first, no previous treatment is necessary in its preparation, so where salvarsan is not needed, inconvenience and expense are avoided; second, the serum can be obtained at any time convenient for the patient and the physician rather than on the exact minute, as is the case with the salvarsanized serum; third, a large supply can be made up at one time and the individual

* Submitted for publication Feb. 5, 1917.

* From the Medical Clinic of the Peter Bent Brigham Hospital.

1. Walker, I. C., and Haller, D. A.: The Treatment of Syphilis of the Central Nervous System with Intravenous Salvarsan Alone, with Intravenous Salvarsan and Intraspinal Salvarsanized Serum Together, and with Intraspinal Salvarsanized Serum Alone, THE ARCHIVES INT. MED., 1916, **18**, 376.

2. Byrnes, C. M.: Jour. Am. Med. Assn., 1914, **63**, 2182.

doses can be used as needed over a period of several weeks, thus saving an enormous amount of labor and time. We were further influenced in trying this method ourselves, as we believed that a comparison of cases treated by the same workers using different methods would be of more value than a comparison of results obtained by different men, because of the uniformity of technic used in the various tests, particularly the Wassermann reactions, and because of a constant personal equation in judging results obtained. It was possible also to use the mercurialized serum in the treatment of patients who had already received several doses of salvarsanized serum, and in this way form an opinion concerning the degree of reaction caused by the two serums in the same group of patients.

The present paper consists of a description of the preparation of mercurialized serum as used in the cases here reported, and of a tabulation of the results obtained from its use in forty-five patients to whom 150 doses were given, with a comparison of these results and those obtained in previous cases with salvarsanized serum. To facilitate comparison, the cases reported here will be numbered in sequence with those previously reported.

Technic.—In the preparation of mercurialized serum, blood is withdrawn from a vein and allowed to clot. The expressed serum is centrifuged in order to free it from cells. The serum is then pipetted into glass tubes in 8 c.c. amounts, and to each tube is added 0.001 gm. of mercuric chlorid in a 0.1 per cent. aqueous solution. The fluid is agitated for a few moments in order to insure a thorough mixing. The white ring of precipitated albuminate of mercury quickly redissolves in the excess of serum, giving a perfectly clear solution. The tubes are plugged and the serum inactivated for thirty minutes at 56 C. They are then stored away on ice until needed, when they are warmed to body temperature and the serum is administered.

The amount of serum used has seemed to be of relatively little importance, although excessive amounts probably add to the immediate reaction. From 6 to 8 c.c. has been the amount used in most of the doses given in this series, for the reason that about that amount of spinal fluid is usually withdrawn for cell count, globulin and Wassermann tests. The dose of mercuric chlorid has been varied from 0.0005 to 0.002 gm. The degree of immediate reaction is not perceptibly changed by increasing the amount to 0.001 gm., but an increase above this figure has seemed to add materially to the discomfort of the patient. The length of time during which the serum was heated to 56 C. has been varied from twenty minutes to two hours without apparently affecting the degree of reaction. The age of the serum does not perceptibly add to its irritating properties. Several doses kept on ice for eight weeks and more were followed by less disturbance than many which were administered within twenty-four hours after preparation.

The reactions in a given patient following the intraspinal administration of irritating drugs, whether salvarsanized serum or serum to which either mercury or salvarsan has been added, are of the same type and vary only in degree. Headache, slight fever, nausea and general malaise are to be expected, and these symptoms do occur in a moderate number of cases. Severe lightning pains follow treatment

in many cases. They are more apt to occur in patients who have previously been troubled with them; many patients who have had no pains for months or even years, often have them recur after treatment. This immediate reaction ordinarily passes off within twelve to twenty-four hours. In about 10 per cent. of individuals it will last longer, and occasionally, but not often, will necessitate two or three days' stay in the hospital after treatment, and several doses of morphin. In our series of cases severe reactions of this kind have been more than three times as frequent after mercurialized serum than after salvarsanized serum. Two patients have, on the day following treatment with mercurialized serum, developed a stiff neck and positive Kernig sign, with a temperature reaching 102 F. This condition did not persist in either case longer than twenty-four hours and there were no sequelae. Subsequent treatments given to these patients have caused no great disturbance. Occasionally intraspinal treatment with either salvarsanized serum or mercurialized serum will precipitate a gastric crisis in a tabetic patient subject to these attacks. In one instance an attack thus begun lasted for a week. Two patients, on the other hand, who were treated during attacks, have had the attack promptly terminate. This has been repeated on several subsequent occasions with one of these patients. The other has never had a recurrence. Temporary increase in tabetic symptoms, ataxia, difficulty in urination, incontinence and paresthesias may occur in the first two or three days following treatment with either serum, and rarely these symptoms last for a week or two. Only one patient has been greatly troubled, and this trouble was lessened by lengthening the interval between treatments. A patient whose case was diagnosed as general paresis, who had had a complete hemiplegia ten years before, with partial recovery, suffered a sudden and complete paralysis of the same side again following his fifth intraspinal treatment with salvarsanized serum. This confined him to bed for seven weeks. At the present time he walks better and uses his hand and arm as well, if not better, than he did before any treatment. This has been our most alarming experience in a total of 600 intraspinal treatments. It seems fair to say that the immediate reaction following either salvarsanized serum or mercurialized serum is one which can be regulated by dosage. We believe that the reaction following 0.001 of mercuric chlorid in 8 c.c. of normal serum is, as a rule, much more severe than that caused by 20 c.c. of undiluted salvarsanized serum. The unusual complications which occur may follow either, but it is reasonable to assume that they are more apt to occur where the irritation is greatest. In the administration of 150 doses of mercurialized serum we have had about as many of them occur as in 450 treatments with salvarsanized serum. Eleven patients have been treated with at least three doses of each kind of serum. In every case

the reaction has been noticeably more severe following the administration of mercurialized serum.

The dosage and frequency of treatment with mercurialized serum depend altogether on the individual features of each case, just as they do with salvarsanized serum. Certain fairly definite rules can, however, be followed. The first dose with every case should be half strength. Later, when the spinal fluid Wassermann reaction is positive only with large amounts of fluid, treatments should be given at greater intervals. Cases of general paresis, active meningitis and cerebrospinal syphilis stand treatment much better than cases of tabes do. In this group of cases the dose each time can be a maximum one and a minimum interval of time between treatments can be safely

TABLE 1.—To Show the Immediate Effect of an Irritant on the Spinal Fluid Cell Count

Case No.	Date of 1st Lumbar Puncture	Cells per C.mm.	Date of First Treatment	Cells per C.mm.	Date of Second Treatment	Cells per C.mm.	Date of Third Treatment	Cells per C.mm.
			Mercurialized Serum					
94	4/14/16	142	5/22/16	140	5/26/16	300*	.....	...
91	6/17/16	34	6/21/16	30	6/27/16	62	.....	...
81	9/ 2/16	156	9/10/16	145	9/16/16	410*	.....	...
79	.....	...	9/ 5/16	291	9/ 9/16	187	9/11/16	300*
82	.....	...	9/ 4/16	175	9/ 8/16	100	9/12/16	180
100	9/15/16	8	9/18/16	8	10/ 2/16	74	.....	...
101	9/27/16	56	9/29/16	50	10/ 4/16	84	.....	...
			Salvarsanized Serum					
27	10/28/14	100	11/ 4/14	37	11/11/14	165	.....	...
24	8/31/14	3	1/27/15	3	2/ 2/15	87	.....	...
64	10/11/15	37	10/17/15	35	10/28/15	64	.....	...
62	.....	...	1/ 7/15	11	1/12/15	128	1/19/15	216*

* Few red cells also present.

allowed. Several patients with meningitis and cerebrospinal syphilis have been given two treatments intraspinally each week for two or three weeks without severe reactions in any case. Two patients with tabes now under treatment cannot stand the administration of intraspinal serum more often than once in three months.

The immediate effect of either serum on the spinal fluid cell count often is to cause an increase in cells. The cell count then falls during the next few days to a point below the previous count. Occasionally, after a severe reaction, the count goes up considerably and red cells appear in the fluid. This is found much more commonly after the use of mercurialized serum than after salvarsanized serum (see Table 1).

A comparison of the efficacy of the two serums in relieving symptoms and in causing objective changes in signs and in the laboratory findings, offers more difficulties than are encountered in a comparison of the reactions from treatment, for while the individual susceptibility to reaction from intraspinal treatment varies, the amount of treatment needed to accomplish the same result in two different cases with the same diagnosis varies to a still greater degree. Evidently, then, the only fair comparison is a comparison of the general averages in fairly large groups of cases. We have attempted this in several ways which can be best understood by a study of the accompanying tables.

In Table 2 there are thirty patients who received a total of 104 doses of salvarsanized serum in addition to intravenous salvarsan. By subtracting the last cell count from the first listed in each case the total drop in cells for that case is found. The total fall for the 30 cases divided by the total number of doses given shows the fall in cells per dose. This fall in the group treated with salvarsanized serum averaged 14 per treatment. The 15 patients listed in Table 3 received a total of 55 doses of mercurialized serum, and here the average drop in cells per treatment calculated in the same way was 27, or twice that obtained in those patients treated with salvarsanized serum.

In the same way by subtracting the amount of spinal fluid necessary for complete fixation before any treatment, from that necessary after three or four doses of salvarsan and intraspinal serum, the change in the Wassermann reaction in cubic centimeters induced by treatment is found. In the cases of Table 2 this averaged 0.04 c.c. per treatment. The average in the second group treated with mercurialized serum was 0.08 c.c., or again twice as great an average change as that induced by salvarsanized serum. In the last column of this table remarks are found which bear on the clinical changes. The comparison here is somewhat in favor of the salvarsanized serum, as all the patients in Table 2 showed indications of improvement, or at least of remission of symptoms. Two patients treated with salvarsan and mercurialized serum showed no change. One of these was a case of general paralysis, the other was a case of tabes dorsalis with gastric crises.

Twenty-seven patients have been treated by the intraspinal route alone. Of these, seventeen were given salvarsanized serum and ten mercurialized serum. The findings in the spinal fluid with the changes resulting from the first three or four treatments are tabulated in Table 4.

The average drop in cell count per treatment in those patients given salvarsanized serum was twenty-one, while the average in those given mercurialized serum was twenty-six, or practically the same figure (Tables 4 and 5). The average change in the strength of the Wasser-

TABLE 2.—To Show the Effect of Three or Four Doses of Intravenous Salvarsan and Intraspinal Salvarsanized Serum on the Cell Count, the Wassermann Reaction, and the Clinical Symptoms

Case No.	Cell Count	Salvar., Gm.	Serum, C.c.	Cell Count	Salvar., Gm.	Serum, C.c.	Cell Count	Salvar., Gm.	Serum, C.c.	Cell Count	Salvar., Gm.	Serum, C.c.	Cell Count	Change in Wassermann Reaction in C.c.	Remarks
29	128	0.3	20	36	0.4	18	25	0.4	20	19	0.4	20	6	0.5 + to 0.8+*	Pain and ataxia less
21	106	0.3	20	11	0.4	20	16	0.4	20	..	...	..	..	0.05+ to 0.1+	Headache and paresthesia relieved
11	145	0.3	14	90	0.4	22	30	0.5	18	10	0.4	20	6	0.05+ to 0.2+	Headache, aphasia and diplopia relieved
15	108	0.4	16	..	0.4	18	..	0.5	20	31	...	..	..	None	Incontinence and ataxia less
17	90	0.4	14	47	0.5	20	13	0.5	20	15	0.5	22	5	0.2 + to 0.3+	Pain relieved; ataxia less
18	84	0.4	20	40	0.4	20	16	0.4	23	10	0.4	26	10	0.2 + to 0.3+	Mentally improved
26	86	0.4	20	63	0.5	20	40	0.6	20	30	0.6	22	32	0.2 + to 0.3+	Pain relieved
29	87	0.3	18	86	0.6	18	15	0.4	25	11	...	..	..	0.1 + to 0.2+	Ataxia and paresthesia relieved
1	35	0.4	18	7	0.5	20	2	0.6	16	1	0.6	20	1	None	Incontinence relieved
6	32	0.3	20	30	0.4	20	20	0.5	18	10	...	..	..	0.2 + to 0.3+	Pain relieved
45	14	0.6	16	5	0.6	18	4	0.5	25	..	...	..	..	1.0 + to 1.0—	Paresthesia relieved
48	37	0.2	18	16	0.4	20	25	0.6	18	8	0.6	20	1	0.2 + to 0.5+	All symptoms relieved
44	33	0.5	20	21	0.5	22	30	0.4	20	20	0.5	20	..	None	All symptoms except ataxia relieved
41	45	0.3	20	17	0.6	25	..	0.6	26	7	...	18	1	0.3 + to 0.6+	Tremor relieved; mentally improved
42	40	0.3	18	33	0.4	22	15	0.4	26	10	0.4	22	1	0.1 + to 0.3+	Gastric symptoms relieved
13	43	0.5	20	13	0.6	20	10	0.6	10	5	...	..	..	0.05+ to 0.2+	Pain, headache and dizziness relieved
20	57	0.6	18	16	0.5	20	16	0.5	22	7	...	..	..	0.3 + to 0.4+	Pain and vomiting relieved
10	47	0.6	16	55	0.6	18	28	0.5	20	16	0.5	20	5	0.2 + to 0.4+	Ataxia relieved
14	35	0.4	20	26	0.5	20	20	0.5	20	16	0.5	25	5	0.1 + to 0.2+	Pain and vomiting relieved
19	18	0.4	16	9	0.5	18	5	0.4	20	5	0.4	18	3	None	Pain and dizziness relieved
8	62	0.4	18	34	0.5	20	9	0.6	18	5	...	..	..	0.3 + to 0.4+	Headache and dizziness relieved
9	25	0.4	20	20	0.5	22	8	0.5	20	7	...	..	..	0.3 + to 0.4+	Pain relieved
5	26	0.4	20	9	0.6	20	10	0.6	18	9	...	..	..	0.2 + to 0.3+	Pain relieved
16	16	0.3	18	10	0.5	20	3	0.4	16	3	0.6	23	..	None	Pain and dizziness relieved
65	36	0.3	20	29	0.5	25	6	0.6	20	4	0.4	20	3	0.1 + to 0.8+	Diplopia relieved; mentally improved
47	21	0.3	20	7	0.4	25	3	0.4	26	1	0.4	20	6	0.2 + to 0.3+	Pain relieved
40	18	0.3	18	11	0.5	20	16	0.4	28	15	0.4	..	..	0.2 + to 0.5+	Ataxia lessened
64	64	0.4	23	30	0.4	20	9	...	20	..	...	..	..	0.5 + to 0.6+	Pain relieved
51	29	...	16	32	0.3	21	20	0.4	22	9	...	..	..	0.4 + to 0.6+	Pain relieved
74	16	0.6	18	5	0.6	15	2	...	..	..	...	..	..	0.2 + to 0.4+	Pain relieved

* Throughout this paper + means "complete fixation."

TABLE 3.—To Show the Effect of Three or Four Doses of Intravenous Salvarsan and Intraspinal Mercurialized Serum on the Cell Count, the Wassermann Reaction, and the Clinical Symptoms

Case No.	Cell Count	Salvar., Gm.	Mercury, Gm.	Cell Count	Salvar., Gm.	Mercury, Gm.	Cell Count	Salvar., Gm.	Mercury, Gm.	Cell Count	Salvar., Gm.	Mercury, Gm.	Cell Count	Change in Wassermann Reaction in C.c.	Remarks
75	15	0.3	0.001	27	0.4	0.001	7	0.4	0.001	7	0.4	0.001	4	None	All symptoms relieved
76	60	0.4	0.001	32	0.9 neo	0.001	10	0.9 neo	0.001	6	0.6	0.001	7	0.1+ to 0.2+	Pain relieved; ataxia lessened
77	60	0.3	0.001	25	0.4	0.001	6	0.4	0.001	23	0.4	0.001	16	0.2+ to 0.8+	Pain and dizziness relieved
78	520	0.3	0.001	201	0.6	0.001	107	0.6	0.001	94	0.6	0.001	15	0.6+ to 0.8+	All symptoms relieved
79	291	0.4	0.001	187	0.6	0.001	300	0.6	0.001	114	0.6	0.001	74	0.2+ to 1.0+	Aphasia gone; vomiting stopped
80	44	0.3	0.001	15	0.4	0.001	2	0.4	0.001	2	0.4	0.001	..	0.1+ to 0.2+	Less pain
81	156	0.4	0.001	410	0.4	0.001	142	0.4	0.001	73	0.4	0.001	42	None	Headaches relieved
82	175	0.6	0.001	100	0.6	0.001	118	0.6	0.001	56	0.6	0.001	45	None	Great mental improvement
83	52	0.4	0.001	30	0.6	0.001	11	0.6	0.001	5	0.6	.....	..	0.2+ to 0.6+	Less pain; no vomiting
84	66	0.4	0.001	40	0.4	0.001	41	0.4	0.001	20	0.4	0.001	20	0.1+ to 0.5+	Headache and vomiting gone
85	36	0.4	0.001	36	0.6	0.001	27	0.6	0.001	5	...	.....	..	0.2+ to 0.3+	No change
86	71	0.4	0.001	31	0.6	0.001	21	0.6	0.001	12	0.6	0.001	..	0.2+ to 0.4+	Pain relieved
87	11	0.6	0.0005	10	0.6	0.001	5	0.6	0.001	3	...	.....	..	0.4+ to 0.5+	Pain lessened
88	136	0.3	0.001	130	0.6	0.001	10	0.4	0.001	3	...	.....	..	0.3+ to 0.5+	Headache and gastric symptoms relieved
101	56	0.4	0.001	20	0.6	0.001	84	0.4	0.001	5	...	.....	..	0.2+ to 0.6+	No change

TABLE 4.—To Show the Effect of Three or Four Doses of Intraspinal Salvarsanized Serum Alone on the Cell Count, the Wassermann Reaction and the Clinical Symptoms

Case No.	Cell Count	Salvar. Serum, C.c.	Cell Count	Salvar. Serum, C.c.	Cell Count	Salvar. Serum, C.c.	Cell Count	Change in Wassermann Reaction in C.c.	Remarks
26	40	15	30	25	14	27	5	None	Pains relieved
27	210	14	100	27	37	20	165	0.4+ to 0.5+	Pains relieved; ataxia less
34	52	16	26	20	30	18	5	0.1+ to 0.2+	Pain and dizziness relieved
25	20	15	3	30	3	25	0	None	Pain and dizziness relieved
4	15	20	10	20	9	20	4	0.4+ to 0.5+	Pain and headache relieved
38	103	20	48	20	40	18	27	0.2+ to 0.3+	Pain relieved
22	7	20	6	15	6	20	6	0.5+ to 0.6+	Pain relieved; ataxia less
24	7	14	5	30	3	21	3	0.4+ to 0.6+	Temporary relief from gastric crises
53	5	15	3	20	3	20	1	0.6+ to 0.9+	Pain and numbness relieved
32	60	20	23	18	11	20	..	1.0 negative	Pain and headache relieved
31	27	15	13	20	7	25	..	1.0 negative	Pain relieved and ataxia lessened
12	43	15	20	20	9	20	..	0.3+ to 0.4+	Headache relieved
35	150	20	75	20	20	20	12	None	Headache and diplopia relieved
23	533	20	272	20	100	25	46	0.1+ to 0.2+	All symptoms relieved
64	20	16	9	20	15	25	3	0.5+ to 0.8+	Pain relieved
66	29	15	16	15	12	20	10	None	Pain relieved
80	16	16	11	20	11	20	5	0.6+ to 0.7+	Pain relieved

TABLE 5.—To Show the Effect of Three or Four Doses of Intraspinal Mercurialized Serum Alone on the Cell Count, the Wassermann Reaction and the Clinical Symptoms

Case No.	Cell Count	Mercury, Gm.	Cell Count	Mercury, Gm.	Cell Count	Mercury, Gm.	Cell Count	Change in Wassermann Reaction in C.c.	Remarks
90	107	0.001	58	0.001	26	0.001	16	0.2+ to 1.0 Neg.	Gain in weight; less ataxia
91	34	0.001	30	0.001	62	0.001	8	No change	No change
92	27	0.001	18	0.001	3	0.001	4	0.4+ to 0.8+	Relief of all pain
93	70	0.001	25	0.001	15	0.001	7	0.3+ to 0.6+	No change
94	142	0.001	300	0.001	26	0.001	20	0.2+ to 0.5+	Relief of pain and dizziness
95	100	0.001	30	0.001	12	0.001	7	0.5+ to 1.0+	Pain relieved
96	44	0.001	0	0.001	2	.....	..	No change	All symptoms relieved
97	6	0.001	6	0.001	2	0.001	3	0.3+ to 1.0 Neg.	All symptoms lessened
98	200	0.001	42	0.001	..	.....	..	No change	Pain lessened
99	20	0.001	6	0.001	..	.....	..	No change	Pain relieved

mann reaction per treatment interpreted as before in cubic centimeters of spinal fluid necessary for complete fixation was 0.03 in those treated with salvarsanized serum. In those treated with mercurialized serum the average was 0.13, or more than four times as great a change. From these figures it appears that mercurialized serum in this dose is a more efficient antisyphilitic than salvarsanized serum as measured by a drop in the strength of the Wassermann reaction. It appears, however, from the preceding comparison of the reactions produced by the two serums that mercurialized serum is so much more irritating that it cannot be used with the frequency with which salvarsanized serum can, and this is especially true of its use in tabes dorsalis. Consequently, the results at the end of a year of treatment, if each serum were used to the greatest extent consistent with safety, probably would not show such a discrepancy against salvarsanized serum because of the larger number of doses which could be given.

A comparison of the ultimate results obtained with the individual cases in the two groups is impracticable because of the differences in the total amount of treatment which has been given to the two groups, and also because of the small interval of time which has elapsed since treatment was discontinued, or because many of the group treated with mercurialized serum are still under treatment. The condition of the individual cases can best be described individually, and this is done in the case reports.

CONCLUSIONS

1. The irritating effect in the spinal canal of serum to which mercuric chlorid has been added in the dose of 0.001 gm. is greater than that of 20 c.c. of salvarsanized serum separated from blood drawn thirty minutes after a dose of 0.6 gm. of salvarsan.

2. The average effect on the laboratory findings in the spinal fluid from one dose of mercurialized serum is greater than from one dose of salvarsanized serum.

3. Unpleasant symptoms are more common following intraspinal mercurialized serum than following salvarsanized serum.

4. The greater irritation of the meninges from mercurialized serum prevents as rapid repetition of dosage as is possible with salvarsanized serum.

5. Cases of general paresis, meningitis and cerebrospinal syphilis stand intraspinal treatment with mercurialized serum better than do cases of tabes dorsalis. It is particularly in cases of active syphilis of the meninges that the mercurialized serum is useful.

6. Mercurialized serum has an advantage over salvarsanized serum in ease of preparation and in its keeping qualities. For these reasons

it can be used under clinical conditions in which the use of salvarsanized serum is impossible, or at least very much more difficult.

REPORT OF CASES

CASE 75.—A man, aged 48, entered the hospital March 27, 1916. A diagnosis of tabes dorsalis was made. Twenty-seven years before he had had gonorrhea. He had had no treatment for syphilis and did not know of his infection. For two years he had had attacks of nausea and vomiting lasting for from eight to ten days, coming on about every month. He had had a chronic deforming arthritis for several years.

Physical examination showed unequal, irregular pupils which did not react to light. His knee jerks were present and equal. There was no Romberg sign. Both elbows were partially flexed and almost completely fixed in that position.

The Wassermann reaction in the blood serum was positive. The spinal fluid gave a positive Wassermann reaction and showed a cell count of 15 per c.mm.

He was given five doses of salvarsan and five intraspinal treatments with mercurialized serum. Two months after his first treatment he became free from gastric symptoms and has remained so up to the present time. The Wassermann reaction was unchanged in his blood and spinal fluid. The cell count in the spinal fluid became normal.

CASE 76.—A man, aged 51, entered the hospital March 25, 1916. A diagnosis of tabes dorsalis was made. He had had a chancre twenty years before. He had had shooting pains in his legs for eight years. For two years he had been ataxic and for one year had had incontinence of urine. For six months he had had girdle sensation. He had lost 18 pounds in weight. His condition had not been influenced by repeated intravenous injections of salvarsan, mercury inunctions and potassium iodid by mouth.

Physical examination showed Argyll Robertson pupils, absent knee and ankle jerks and a positive Romberg sign.

The Wassermann reaction was positive in both blood serum and spinal fluid, with a spinal fluid cell count of 60 per c.mm. He was given six intravenous doses of salvarsan and five intraspinal treatments with mercurialized serum. His pains became less severe after two treatments; after five they were almost absent. His girdle sensation disappeared. The ataxia was somewhat lessened. The Wassermann reaction in his blood serum was unchanged, in his spinal fluid it had changed by only 0.1 c.c. The cell count had fallen to 7 per c.mm.

CASE 77.—A man, aged 42, entered the hospital April 5, 1916. A diagnosis of cerebrospinal syphilis was made. In 1904 he had had a chancre. Eight months before entrance he had had a sudden complete paralysis of his right side, with inability to speak for two weeks, and retention of urine. The paralysis had slowly cleared up until he was able to walk about his room, but could do very little more. He had had pain in his neck and both arms, which was gradually becoming more severe.

Physical examination showed small, irregular pupils, which did not react to light. There was some muscle atrophy of the right side, with decided weakness of his right arm and leg. All reflexes on that side were increased and there was a positive ankle clonus, Babinski, Gordon and Oppenheim.

The Wassermann reaction in both blood and spinal fluid was positive. The spinal fluid also gave a positive globulin test and showed a cell count of 60 per c.mm.

He was given four doses of salvarsan intravenously, large amounts of potassium iodid and some mercury. He was also given six doses of mercurialized serum intraspinally. At the end of six months all pain had gone from his neck and arms, he could walk better, but still dragged his leg. His right arm was gradually recovering some power and he was doing part time work with the fire department.

His blood serum continued to give a positive Wassermann test. His spinal fluid showed a cell count of 5 per c.mm., and gave a positive Wassermann test with 0.8 c.c. whereas at entrance only 0.2 c.c. was required for complete fixation.

CASE 78.—A man, aged 36, entered the hospital Aug. 28, 1916. A diagnosis of syphilitic meningitis was made. He had never had any previous syphilitic lesions. For two months he had had frequent headaches. Five days before entrance he had had extreme headache, failing vision, increasing mental confusion, vomiting and stiffness of his neck.

Physical examination showed a general hyperesthesia, stiff neck, with pain on motion, bilateral Kernig's sign and increased reflexes. There was some mental confusion.

The Wassermann reaction was positive in both blood and spinal fluid. The spinal fluid showed a cell count of 520 per c.mm. and gave a positive globulin test. His temperature was 103 F., pulse 100 per minute and respirations 30. The white blood count was 8,400 per c.mm.

After three weeks of treatment there were no signs of meningitis remaining, the patient was free from all symptoms and was out of bed all day. He was given eight doses of salvarsan intravenously in addition to potassium iodid and mercury. He was also given six doses of mercurialized serum intraspinally. His blood Wassermann reaction continued to be positive. His spinal fluid showed a normal cell count and gave a negative Wassermann reaction and globulin test. Six weeks after he entered the hospital he returned to work and had been working steadily ever since.

CASE 79.—A man, aged 22, entered the hospital Sept. 4, 1916. A diagnosis of cerebrospinal syphilis was made. He had had a chancre five years before and had been given three doses of salvarsan intravenously. He had had no further symptoms until six months before entrance to the hospital when he had begun to have some stomach trouble and headache. These symptoms had partially cleared up after further intravenous salvarsan. One day before entrance he had suddenly lost his faculty of speech and ability to swallow and the right side of his face had become paralyzed. He had had almost constant vomiting and hiccough since that time.

Physical examination showed unequal pupils, which reacted poorly to light, a right facial paralysis and a partial paralysis of his tongue and the muscles of deglutition. There was a double Kernig's sign but no stiffness of the neck. Fundus examination showed considerable edema of both disks. There was complete aphonia, frequent vomiting and continual hiccough.

The Wassermann reaction was positive in both blood and spinal fluid. The spinal fluid showed a cell count of 300 per c.mm. and gave a positive globulin test.

Treatment consisted of mercury intramuscularly, large doses of potassium iodid by mouth, seven doses of salvarsan intravenously and seven intraspinal treatments with mercurialized serum. Two months after the first treatment his blood serum gave a weakly positive test. His spinal fluid gave a positive Wassermann reaction with 1.5 c.c., whereas at first only 0.2 c.c. was required for complete fixation. The cell count had fallen from 300 per c.mm. to 20. He showed no signs of his trouble except a slight drooping of the right angle of his mouth.

CASE 80.—A woman, aged 36, entered the hospital June 12, 1916. A diagnosis of general paresis of the insane was made. She had been married nineteen years and had one child 18 years old. She had had four miscarriages. Her husband had had general paralysis of the insane for more than two years and had been recently committed to a home for the insane. She had had pains in her legs for three years, attacks of dizziness for one year and had had numbness and paresthesia of her legs for six months.

Physical examination showed unequal and irregular pupils, which did not react to light. The knee and ankle jerks were equal but exaggerated. She

showed very definite mental instability and cried or laughed on the slightest provocation. There was some memory defect.

The Wassermann reaction was positive in both blood serum and spinal fluid. The spinal fluid showed a cell count of 44 per c.mm. and gave a positive globulin test.

She was given four doses of mercurialized serum intraspinally and six doses of salvarsan intravenously without change in her symptoms other than relief of pain.

The Wassermann reaction remained unchanged in either blood or spinal fluid. The spinal fluid cell count fell from 44 to 2 per c.mm.

Case 81.—A woman, aged 22, entered the hospital Sept. 2, 1916. A diagnosis of cerebrospinal syphilis was made. She had had poor health all of her life. At the age of 5 she had had a rash on her face diagnosed as syphilis. One year later she had had syphilitic periostitis of both tibiae and two years later she had had syphilitic iritis of the right eye. Six months before entrance she had had general malaise, drowsiness, apathy, anorexia, numbness of her hands, headache, vertigo, polyuria, polydypsia and had lost 15 pounds of weight.

Physical examination showed the scars of an old iritis on the right, with ability to count fingers at 1 foot. Vision in the left eye was normal and the right pupil was regular and reacted to light. The tibiae showed marked changes due to syphilitic osteitis and periostitis. The urine was always of light color, with specific gravity of 1.005 and lower. The twenty-four-hour amount was usually about 2,000 c.c. The Wassermann reaction was positive in both blood and spinal fluid. The spinal fluid gave a positive globulin test and showed a cell count of 148 per c.mm.

Treatment consisted of five doses of mercurialized serum intraspinally and seven doses of salvarsan intravenously in addition to mercury intramuscularly and large doses of potassium iodid by mouth. After three weeks of treatment all headaches, dizziness, drowsiness and anorexia disappeared. She felt well and began to gain weight. Later the numbness of her hands disappeared. Treatment had no effect on her urinary symptoms.

The Wasserman reaction remained unchanged in both blood and spinal fluid. The spinal fluid cell count had fallen from 148 per c.mm. to 42 per c.mm.

Case 82.—A man, aged 32, entered the hospital Jan. 13, 1916. Nine months before entrance he had had a chancre which was followed by a rash and sore throat, and at that time his blood Wassermann reaction had become positive. Two months after infection he had developed headache and dizziness. Three doses of neosalvarsan and fifty doses of intramuscular mercury had to some extent relieved his symptoms, but they had lately recurred and had progressed rapidly. At the time of admission he showed that he was below par mentally, with a marked memory defect. His replies to questions were vague and indefinite.

Physical examination showed unequal pupils which reacted to light. Fundus examination showed a one diopter choked disk on each side, with overfilled and tortuous veins. The deep reflexes were unchanged.

The Wassermann reaction in the blood serum was positive.

A right subtemporal decompression was performed and 10 c.c. of salvarsanized serum were injected into the lateral ventricle. The ventricular fluid removed gave a positive Wassermann reaction with 0.05 c.c., a positive globulin test, and showed a cell count of 230 per c.mm. Three days later the spinal fluid showed 240 cells per c.mm. and gave a positive Wassermann reaction with 0.05 c.c. He was given three doses of salvarsan at weekly intervals and sent home for further treatment there. Six months later he was again admitted to the hospital. At this time he was dull and stupid, disoriented for time and place, and could not answer questions in an intelligent manner. He showed also great fear when left alone. His blood Wassermann reaction was positive.

The spinal fluid cell count was 175 per c.mm., there was an excess of globulin and the Wassermann reaction was positive with 0.05 c.c.

He was given ten doses of mercurialized serum intraspinally and ten doses of salvarsan in addition to mercury inunctions and very large doses of potassium iodid by mouth. After five treatments a great change was noticeable in his condition. After his tenth treatment he was free from symptoms and seemed perfectly normal mentally.

There was no change in his blood Wassermann reaction. The Wassermann reaction in his spinal fluid changed from positive with 0.05 to positive with 0.2 c.c. The cell count fell from 175 per c.mm. to 9 per c.mm.

Case 83.—A man, aged 38, was admitted to the hospital, Aug. 14, 1916. A diagnosis of tabes dorsalis was made. Eighteen years before he had had a chancre. For four years he had had infrequent attacks of nausea, with eructations of gas. For six weeks he had had constant pain in the epigastrium, which bore no relation to meals or time of day. He had become weak and tired and had lost 4 pounds in weight.

Physical examination showed unequal and irregular pupils, which did not react to light. The deep reflexes were unchanged. The Wassermann reaction in both blood and spinal fluid was positive. The spinal fluid gave a positive globulin test and showed a cell count of 52 per c.mm.

He was given three doses of mercurialized serum intraspinally and five intravenous doses of salvarsan. He has had no abdominal pain and no gastric symptoms since his second treatment.

The Wassermann reaction in the blood serum was not affected by treatment. The spinal fluid Wassermann reaction changed from positive with 0.2 c.c. to positive with 0.6 c.c. The spinal fluid cell count fell from 52 to 5 per c.mm.

Case 84.—A woman, aged 47, entered the hospital Aug. 22, 1916. A diagnosis of general paralysis of the insane was made. She had had a syphilitic sore throat fifteen years before. For one year she had anorexia and vomiting after meals. For six months she had had headache, dizziness and increasing difficulty in walking. One week before entrance she had had a period of aphonia which lasted for nine hours. For several days she had had severe pains in the legs and a sense of constriction about her neck.

Physical examination showed tenderness to pressure over the whole skull. The pupils were unequal and did not react to light. The arm reflexes were very active. Knee and ankle jerks were diminished, but were present on both sides. There was marked swaying in the Romberg position. Gag reflex was absent.

The Wassermann reaction in both blood serum and spinal fluid was positive. The spinal fluid gave a positive globulin test and showed a cell count of 66 per c.mm.

Treatment consisted of five doses of mercurialized serum intraspinally, six doses of salvarsan intravenously, mercury and potassium iodid by mouth. After the second intraspinal treatment she claimed to be entirely free from symptoms.

The Wassermann reaction in the blood serum was unchanged. The spinal fluid Wassermann reaction changed from positive with 0.1 c.c. to positive with 0.5 c.c. The cell count fell from 66 to 20 per c.mm.

Case 85.—A man, aged 48, entered the hospital Sept. 8, 1916. A diagnosis of general paralysis of the insane was made. He had had a chancre twenty years before. He had lost 30 pounds in the last five years. For one year he had had dizziness, nervousness and tremor of the muscles of his face.

Physical examination showed irregular pupils, which did not react to light. Knee jerks were present but unequal. He was dull mentally and had some memory defect.

Wassermann reaction in both blood serum and spinal fluid was positive. The spinal fluid gave positive globulin test and showed a cell count of 36 per c.mm.

He was given three doses of mercurialized serum intraspinally and four doses of salvarsan intravenously. There was no change in his condition from treatment. The Wassermann reaction in his spinal fluid changed from positive with 0.2 c.c. to positive with 0.3 c.c. The cell count fell from 36 to 5 per c.mm.

CASE 86.—A man, aged 35, entered the hospital Aug. 21, 1916. A diagnosis of tabes dorsalis was made. He had had gonorrhea twice, but denied having had syphilis. For nine years he had had paroxysmal attacks of pain in both shoulders, and for two years had had pain of the same kind in both legs, with parasthesias.

Physical examination showed irregular, unequal pupils, which did not react to light, and sluggish deep reflexes in both arms and legs.

The Wassermann reaction was positive in both blood and spinal fluid. The spinal fluid showed a cell count of 71 per c.mm. and gave a positive globulin test.

He was given four doses of mercurialized serum intraspinally and five doses of salvarsan intravenously. The Wassermann reaction was unchanged in his blood. The spinal fluid changed from positive with 0.2 c.c. to positive with 0.4 c.c. The cell count fell from 71 per c.mm. to 12 per c.mm. He was entirely relieved from pain and parasthesias after the third treatment.

CASE 87.—A man, aged 29, entered the hospital June 8, 1916. A diagnosis of rheumatic fever and tabes dorsalis was made. He had had rheumatic fever at the age of 18 and again at 26. He had had a chancre three years before entrance. He had had shooting pains in the back of his neck and head for six months.

Physical examination showed an acute arthritis of both knees and one shoulder. These manifestations promptly disappeared after a few days in the hospital. In addition he showed absent knee and ankle jerks, unequal and irregular pupils, which reacted poorly to light.

The Wassermann reaction in both blood and spinal fluid was positive. The spinal fluid showed a cell count of 11 per c.mm. and gave a positive globulin test.

He was given five doses of salvarsan intravenously without any change in symptoms or change in his spinal fluid cell count. After his first dose of mercurialized serum the cell count fell to normal. He had two additional doses of mercurialized serum intraspinally and six additional doses of salvarsan intravenously. His blood Wassermann reaction became negative and he became free from symptoms. The Wassermann reaction in his spinal fluid was unchanged.

CASE 88.—A woman, aged 28, entered the hospital Aug. 23, 1916. A diagnosis of cerebrospinal syphilis was made. She had had syphilis for four years. For two years she had had severe headaches and failing vision in her right eye, and for one year she had had nausea and vomiting whenever she had undertaken any physical exertion. For six months she had been very irritable, and for one month had been almost continuously in bed.

Physical examination showed unequal pupils, which did not react to light.

The Wassermann reaction was positive in both blood and spinal fluid. The spinal fluid cell count was 136 per c.mm.

She was given three doses of mercurialized serum intraspinally and six doses of salvarsan intravenously. This relieved her of all symptoms.

Her blood Wassermann reaction had not changed. The spinal fluid Wassermann reaction changed from positive with 0.3 c.c. to positive with 1.5 c.c. The spinal fluid cell count fell from 136 to 3 per c.mm.

CASE 89.—A woman, aged 48, entered the hospital June 27, 1916. A diagnosis of cerebrospinal syphilis was made. For two years she had had weakness of the legs and ataxia. For one year she had had headaches and for six weeks she had had such extreme headaches, dizziness and vomiting that she had been confined to bed.

Physical examination showed normal pupils, increased and unequal knee jerks, an ankle clonus on the right, and a positive Babinski's sign.

The Wassermann reaction in both blood and spinal fluid was positive. The spinal fluid cell count was 15. She was given three doses of salvarsan intravenously and two doses of mercurialized serum intraspinally. The blood Wassermann reaction was unchanged. The spinal fluid cell count fell from 15 to 6 per c.mm., and the Wassermann reaction changed from positive with 0.1 c.c. to positive with 0.4 c.c. This amount of treatment entirely relieved her of headaches and vomiting, the dizziness was greatly lessened and she was able to walk around without difficulty.

CASE 90.—A man, aged 42, entered the hospital March 4, 1916. A diagnosis of tabes dorsalis was made. For two years he had had numbness and weakness in his legs and for three months he had had unsteadiness in his gait.

Physical examination showed unequal pupils, which did not react to light, absent knee and ankle jerks, ataxia of the legs and a positive Romberg's test.

The Wassermann reaction in the blood serum was negative. The spinal fluid showed 107 cells per c.mm. and gave a positive Wassermann reaction.

He was given six doses of mercurialized serum intraspinally. Eight months after the treatment the numbness had disappeared from his legs and they became much stronger. Ataxia was lessened and he had gained 8 pounds weight.

CASE 91.—A man, aged 47, entered the hospital June 22, 1916. A diagnosis of general paralysis of the insane was made. He had had syphilis twenty-five years before. Five years before he had had a nervous breakdown and had become unsteady on his feet. For nine weeks he had had tenderness and pain in his left hand and for three weeks incontinence of urine.

Physical examination showed unequal pupils, which reacted poorly to light, exaggerated deep reflexes, a positive Romberg and a Babinski on each side. There was weakness and atrophy of the left hand, arm and leg, with disturbed sensation over the hand and arm.

The Wassermann reaction in the blood serum was negative. The spinal fluid showed a cell count of 34 per c.mm. and gave a positive Wassermann test with 0.5 c.c. He was given two intravenous doses of salvarsan and five intraspinal injections of mercurialized serum. The Wassermann reaction in his spinal fluid became more strongly positive under treatment, so that only 0.3 c.c. were required for complete fixation. The cell count fell to 4 per c.mm. There was little improvement in his condition clinically. He regained control of his urine and the pain in his hand became less severe.

CASE 92.—A woman, aged 48, entered the hospital March 20, 1916. A diagnosis of tabes dorsalis was made. She had had syphilis for eighteen years. For nine years she had had frequent pains in her legs. For six years she had had transient attacks of diplopia. She had had one dose of salvarsan and a great deal of mercury and potassium iodid without any relief.

Physical examination showed normal pupils and hyperactive deep reflexes in legs and arms.

The Wassermann reaction was negative in the blood. The spinal fluid showed 27 cells and gave a positive Wassermann reaction with 0.4 c.c.

She was given five doses of mercurialized serum intraspinally. The Wassermann reaction in the spinal fluid became negative, the cell count fell to 2 per c.mm. and she became entirely symptom-free.

CASE 93.—A man, aged 42, entered the hospital Aug. 31, 1916. A diagnosis of tabes dorsalis was made. For one year he had had difficulty in walking at night, urinary disturbance, sharp pains in his legs, occasional attacks of diplopia and rapidly increasing deafness. Eight months before he had fallen and broken his leg. He had lost 21 pounds weight in the last year.

Physical examination showed unequal, irregular pupils, which did not react to light, absent knee and ankle jerks, marked ataxia of hands and feet, double vision and almost total deafness.

The Wassermann reaction in the blood serum was negative. The spinal fluid showed 70 cells per c.mm. and gave a positive Wassermann test with 0.3 c.c.

He was given five doses of mercurialized serum intraspinally. The Wassermann reaction in the spinal fluid changed from positive with 0.3 c.c. to positive with 0.6 c.c. The cells fell from 70 to 7 per c.mm. There was no change in any of the patient's symptoms.

CASE 94.—A man, aged 48, entered the hospital May 15, 1916. A diagnosis of tabes dorsalis was made. He had had urinary disturbances for eighteen months and had lost 18 pounds weight during the same time. He had had pains in his legs for six months.

Physical examination showed unequal and irregular pupils, which did not react to light; unequal knee jerks; swaying in the Romberg position; tremor of the hands and some ataxia.

The Wassermann reaction in the blood serum was negative. The spinal fluid showed a cell count of 142 per c.mm. and gave a positive Wassermann reaction.

He was given seven doses of mercurialized serum intraspinally. The Wassermann reaction in his spinal fluid changed from positive with 0.2 c.c. to positive with 0.7 c.c. The spinal fluid cell count fell from 142 to 15 per c.mm. All his symptoms disappeared after the sixth treatment.

CASE 95.—A man, aged 42, entered the hospital May 6, 1916. A diagnosis of tabes dorsalis was made. For six years he had had lightning pains in his legs, which gradually became more severe and frequent. Mercury and potassium iodid by mouth had given no relief.

Physical examination showed irregular pinpoint pupils, which did not react to light; areas of hyperesthesia over the lower back; hyperactive reflexes in both arms and legs.

The Wassermann reaction in the blood was negative. The spinal fluid gave a positive Wassermann reaction with 0.5 c.c. and showed a cell count of 100 per c.mm.

He was given six doses of mercurialized serum intraspinally. The Wassermann reaction changed from positive with 0.5 c.c. to positive with 1.5 c.c. The cell count fell from 100 to 4 per c.mm. The pains were greatly lessened after only three treatments and after six treatments they almost entirely disappeared.

CASE 96.—A woman, aged 38, entered the hospital Aug. 4, 1916. A diagnosis of tabes dorsalis was made. One year before she had had both fallopian tubes removed because of gonococcus infection. For six months she had had attacks of sharp epigastric pain and vomiting coming on about once in three weeks. The attacks had been relieved only by morphin.

Physical examination showed irregular and unequal pupils, which reacted to light, a low, hypotonic stomach and a moderately dilated aorta. The Wassermann reaction in the blood was negative. The spinal fluid gave a cell count of 44 per c.mm.

She was given two doses of mercurialized serum intraspinally. The cell count in the spinal fluid was reduced from 44 to 0 per c.mm. by the first treatment. The Wassermann reaction was not changed. She had no pain or vomiting after treatment was begun.

CASE 97.—A man, aged 48, was admitted to the hospital Feb. 22, 1916. A diagnosis of tabes dorsalis was made. He had had a chancre twenty-six years before. He had been treated for five years for chronic nephritis. For two years before admission he had had difficulty in walking, especially at night, and dizziness. These symptoms had grown worse rapidly, so that for three months he had been almost continually in bed.

Physical examination showed a moderately advanced chronic nephritis with a systolic blood pressure of 210 mm. of mercury. The pupils were irregular and reacted poorly to light. The knee jerks were hyperactive.

The Wassermann reaction in his blood serum was negative. The spinal fluid showed a cell count of 6 per c.mm. and gave a positive Wassermann reaction with 0.3 c.c.

He was given four doses of mercurialized serum intraspinally. The Wassermann reaction in the spinal fluid became negative with 1 c.c. and the cell count fell to 2 per c.mm. After three treatments the dizziness entirely disappeared and he became able to resume his work, which he had not touched for more than two years.

CASE 98.—A man, aged 61, entered the hospital May 24, 1916. A diagnosis of tabes dorsalis was made. For ten years he had had paresthesias of his feet and for two years difficulty in walking, with pains in his legs and thighs.

Physical examination showed Argyll Robertson pupils and absent knee and ankle jerks.

The Wassermann reaction in the blood was negative. The spinal fluid gave a positive reaction with 0.4 c.c., and showed a cell count of 200 per c.mm.

He was given two doses of mercurialized serum intraspinally. The pains in his legs were lessened. The cell count in the spinal fluid fell from 200 to 10 per c.mm. The Wassermann reaction was unchanged.

CASE 99.—A woman, aged 41, entered the hospital Jan. 15, 1916. A diagnosis of general paralysis of the insane was made. She had had syphilis for fourteen years. For three years she had had sharp pains in her extremities and had lost 18 pounds weight during that time. She had had mercury continuously tor six months without any benefit.

Physical examination showed irregular, fixed pupils and unequal knee jerks. She was very talkative and had some memory defect.

The Wassermann reaction in the blood serum was negative. The spinal fluid gave a positive reaction with 0.1 c.c. and showed a cell count of 20 per c.mm. She was given two doses of mercurialized serum intraspinally. The cell count fell to 6 per c.mm. and the Wassermann reaction changed from positive with 0.1 c.c. to positive with 0.5 c.c. All the pains disappeared after the first treatment and did not recur. There was no change in her mental condition.

CASE 100.—A man, aged 50, entered the hospital Sept. 12, 1916. A diagnosis of tabes dorsalis was made. For eight years he had had occasional attacks of epigastric pain, nausea and vomiting. He had had difficulty in walking in the dark for seven years. For six months he had had girdle sensation and pains in his legs.

Physical examination showed unequal irregular fixed pupils; absent knee and ankle jerks; positive Romberg's test and ataxia of both hands and feet.

The Wassermann reaction was negative in the blood and spinal fluid. The spinal fluid also gave a negative globulin test and showed only 8 cells per c.mm. He was given two doses of mercurialized serum intraspinally which caused no change in symptoms, but a rise in the spinal fluid cell count to 74 per c.mm. Two months later the cell count had fallen to 12 per c.mm. and he stated that his pains and girdle sensation had disappeared.

CASE 101.—A man, aged 53, entered the hospital Sept. 7, 1916. A diagnosis of tabes dorsalis was made. He had had attacks of severe abdominal pain with vomiting almost every week for three months.

Physical examination showed Argyll Robertson pupils.

The Wassermann reaction in the blood was positive. The spinal fluid showed a cell count of 56 per c.mm. and gave a positive Wassermann reaction with 0.2 c.c. He was given three doses of mercurialized serum intraspinally and four doses of salvarsan intravenously. The Wassermann reaction in the blood serum was unchanged. The spinal fluid Wassermann reaction was changed from positive with 0.2 c.c. to positive with 0.6 c.c. The cell count fell from 56 to 5 per c.mm. The attacks of vomiting still continue but are not of such duration or frequency as before treatment.

Eleven patients previously treated with salvarsanized serum were each given three or more intraspinal treatments with mercurialized serum, a total of thirty-eight doses. The effect on the Wassermann reaction, cell count and clinical symptoms was in every case equally as good as, if not better than, from the same amount of salvarsanized serum. The reactions in every case were more severe than with the salvarsanized serum.

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THE SALICYLATES

VI. RENAL, FUNCTIONAL AND MORPHOLOGIC CHANGES IN ANIMALS FOLLOWING THE ADMINISTRATION OF SALICYLATE*

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It was previously shown[1] that individuals receiving full therapeutic doses of salicylate invariably have albumin, leukocytes and casts or cast-like bodies in the urine. This albuminuria is produced in both febrile and afebrile individuals, and is of renal origin. The functional tests (phenolsulphonephthalein excretion in urine and nonprotein nitrogen of the blood) which were applied at the time, gave inconstant results, and the changes in some cases were so small that it was impossible to conclude definitely whether any serious impairment in the functional efficiency of the kidney existed. It is possible that repeated administration of salicylate might cause more definite and marked changes in the kidney, both functionally and morphologically. Moreover, in certain individuals, the albuminuria and other changes are so severe that the presence of a definite nephritis is suggestive.

Von Ackeren[2] gave sodium salicylate and salicylic acid per os to five rabbits, and two of these animals showed "acute nephritis," with albuminuria and hematuria. He cites fourteen cases in the literature up to 1890, in which there was albuminuria, sometimes accompanied by hematuria, following administration of salicylate. Vinci[3] observed a toxic parenchymatous nephritis at the necropsy of a man 45 years of age, who died thirty-one hours after the ingestion of 35 gm. of sodium salicylate. There was marked congestion of all the renal vessels, particularly in the glomerular tuft, albuminous precipitate in the subscaplar space, interstitial hemorrhage, cloudy swelling and extensive necrosis of the tubular epithelium, most marked in the cortex;

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1. Scott, R. W., and Hanzlik, P. J.: The Salicylates: III. Salicylate Albuminuria, Jour. Am. Med. Assn., 1916, **67,** 1838.

2. Von Ackeren, A.: Ueber Nierenreizung nach Salicylsäure Gebrauch, Charité Ann., 1890, **15,** 252.

3. Vinci, G.: Sulle lesioni istologiche sperimentali del rene determinate dall acido salicilico con un caso raro di anvelenamento nell uomo salicilato di soda, Arch. di farmacol. sper., 1905, **4,** 59.

but as the necropsy was performed two days after death, June 25, and as the kidneys sent to Vinci were imperfectly preserved in alcohol, little importance can be attached to the histologic findings. Experimenting with dogs, guinea-pigs and rabbits, he found that massive single doses, and frequently repeated large doses, led essentially to the same change as he described in the human kidney. For the most part the drug was given by mouth, but in a few instances was given intravenously or subcutaneously. He states that the lesions were most marked in dogs, less in guinea-pigs and least in rabbits. Lüthje,[4] in addition to a large amount of clinical work, gave repeated doses of sodium salicylate to two dogs, and both showed cylindruria, one showing albuminuria. Busse examined the kidneys and found general congestion, interstitial hemorrhage, cloudy swelling, fatty degeneration, cast formation, and in the subscapular space of the glomerulus a homogeneous coagulum. With the exception of the reports of von Ackeren, Lüthje and Vinci, the literature seems to be devoid of carefully controlled experimental work on the effect of salicylate on the kidneys of lower animals.

The object of this study is to ascertain what effect the administration of salicylate has on the morphology of the kidney and its functional efficiency as judged by certain nitrogenous constituents of the blood in animals subjected to varying conditions of dosage, mode and duration of administration of the drug. Our own work was carried out on dogs, cats and one rabbit. The dosage of salicylate used corresponded to the so-called "toxic" or full therapeutic dose used with human individuals suffering with rheumatic fever, that is, about 0.23 gm. of sodium salicylate (0.2 gm. salicylic acid) per kilo. In some cases only one such dose was administered. In other cases, repeated doses were used with the object of producing a nephritis if possible. Usually, the salicylate (10 per cent. solution in water) was administered hypodermically. In a few instances the drug was also administered by mouth, but oral administration was not generally practiced because of loss of the drug by emesis.

As a rule, the animals were observed for two to three days before the experiment was begun, since they almost invariably showed some evidences of albuminuria. The drug was then injected and careful notes of symptoms, urinary and blood changes were made. Albumin was tested for qualitatively by the heat and acetic acid and ferrocyanid tests. The blood for nitrogen estimations was obtained directly from the heart. Nonprotein nitrogen was estimated according to the method

4. Lüthje, H.: Ueber die Wirkung von Salicylpräparaten auf die Harnwege nebst einigen Bemerkungen über die Genese der Cylinder und Cylindroide, Deutsch. Arch. f. klin. Med., 1902, **74**, 163.

of Folin and Denis,[5] and urea nitrogen by the urease method, using an aqueous extract of jack bean preserved with glycerin,[6] aeration and nesslerization. A microscopic examination of the urine was made regularly for the presence of leukocytes, erythrocytes and casts. In a number of animals the reaction of the blood and the reserve alkalinity before and after the administration of salicylate were estimated according to the methods of Levy, Rowntree and Marriott[7] (reaction of blood) and Marriott[8] (alkali reserve).

The animals were usually killed by a few whiffs of chloroform on the expiration of a given time; necropsy was performed and the kidneys were excised. Small blocks from both organs (about 5 mm. thick) were fixed immediately in Zenker's fluid and in formaldehyd, embedded in celloidin and stained with hemalum and eosin.

The various pertinent data have been summarized in the accompanying table. For further details, the appended brief protocols of all the experiments may be consulted.

DISCUSSION

The data in the table and protocols indicate that the administration of salicylate causes the appearance of albumin, leukocytes, granular casts or cast-like bodies, and sometimes red blood corpuscles in the urine of cats, dogs and one rabbit. When these elements were present before the experiment they were increased by the administration of the drug. This is confirmatory (except appearance of erythrocytes in urine) of what was observed in human beings.

Practically all (ten) of the eleven animals, whose blood was examined, showed a variable though definite accumulation of nonprotein and urea nitrogen, an indication, therefore, of diminished renal functional efficiency so far as these tests are concerned. In Dog 17 certain of the results for urea nitrogen appear rather low. However, repeated determinations confirmed the results. There seems to be, at least in certain individuals, an increase in renal permeability for urea at an early stage in the action of salicylate as indicated by these figures. This phenomenon was previously observed, and apparently is more commonly encountered in human beings. It was partly because of

5. Folin, O., and Denis, W.: New Methods for the Determination of Total Nonprotein Nitrogen, Urea and Ammonia in Blood, Jour. Biol. Chem., 1912, **11,** 527.

6. For this method of preparation of urease we are indebted to Dr. Cyrus H. Fiske of the Biochemical Laboratory.

7. Levy, R. L., Rowntree, L. G., and Marriott, W. McK.: A Simple Method for Determining Variations in the Hydrogen-ion Concentration of the Blood, THE ARCHIVES INT. MED., 1915, **16,** 389.

8. Marriott, W. McK.: A Method for the Determination of the Alkali Reserve of the Blood Plasma, THE ARCHIVES INT. MED., 1916, **17,** 840.

this variability of the effect, that is, function seemed to be favored sometimes, other times diminished, and partly because of the small differences in the results obtained, that it was impossible to decide as to the extent of impairment in kidney function. The study of additional human cases seems to confirm what certainly appears to be the case in animals, namely, a diminution in renal functional efficiency. Just how permanent this change is cannot be definitely stated. In two of the animals there was a tendency for the urea nitrogen of the blood to return to the previous level, and in the majority of those observed over long periods of time the albuminuria gradually diminished.

So far as the reaction and the reserve alkalinity of the blood are concerned, no important changes were observed in the few animals studied.

As to morphologic changes, the data indicate that full therapeutic doses of sodium salicylate are capable of producing in animals definite lesions of the kidney, easily demonstrable by microscopic examination. In the case of Animal 17, oral administration of the drug produced a renal lesion quite as severe, both functionally and morphologically, as followed subcutaneous administration.

Considering the series as a whole, the administration of the drug was followed by histologic lesions varying from slight cloudy swelling of the tubular epithelium to severe cloudy swelling associated in a few cases with necrosis and desquamation, and in nine instances with distinct glomerular lesions. The glomerular lesions were never very severe and consisted principally of swelling and multiplication of capillary endothelium. In these cases the severe involvement of the tubules seemed to justify emphasizing that phase in the diagnosis rather than making a diagnosis of acute glomerular nephritis. The finding of albuminous granular precipitate in the subcapsular space, in the opinion of the writers, does not justify a definite diagnosis of glomerular lesion; accordingly several cases diagnosed as cloudy swelling show in addition this minor change.

The proximal convoluted tubule was apparently the first part attacked followed very rapidly by lesion of the distal convoluted tubule, then of the ascending limb of the loop of Henle. As a rule, it appeared that these divisions were involved before lesion of the glomerulus occurred. In cases in which all these features appeared, the lesion of the proximal convoluted tubule was the most severe change. No stress is laid on fatty changes, because, independently of experimental procedures, such changes are practically constant in the cat and frequent in both the dog and rabbit. The diagnosis of necrosis of tubular epithelium in these kidneys rests in part on finding distinct nuclear pyknosis, and in part on finding desquamation of entire cells and groups of cells. The accompanying figure illustrates a renal lesion.

Although Vinci found differences in the susceptibility of dogs, guinea-pigs and rabbits, the experiments reported in this paper show no material differences in susceptibility of dogs and cats. He found essentially the same type and distribution of tubular lesion as we have described, but in contrast to the definite intracapillary glomerulitis seen in some of our animals, he describes only marked congestion of the tuft. In his series and ours there was found cloudy swelling of glomerular epithelium and albuminous material in the subcapsular

Kidney of Dog 12 showing slight involvement of the glomerular tuft, which, although not enlarged, is richly cellular and devoid of blood. The tubular epithelium shows cloudy swelling and the lumina contain granular albuminous precipitate.

space. Vinci's failure to find the more marked glomerular lesion is probably due to the fact that most of his animals died or were killed after only seven or eight hours.

It is not possible in this series definitely to correlate the morphologic and functional changes. It will be noted as an indication of this difficulty that the most marked accumulation of urea nitrogen occurred in connection with a kidney that histologically showed no change in the

glomeruli except cloudy swelling of the lining epithelium and albuminous precipitate in the subcapsular space (Experiment 4).

An interesting fact, which may or may not have a bearing on the problem of albuminuria and nephritis, is a diminution in the total excretion of salicylate in the urine of Dog 18 as compared with the urinary excretion of Dog 19. The kidney of Dog 18 shows a definite, acute tubular nephritis which, in part, at least, may have been present before the animal received salicylate. Dog 19 was in good condition and the kidneys show cloudy swelling without glomerular change. Relatively, the accumulation of urea nitrogen in the blood of Dog 18 is also greater than that of Dog 19. Whatever the explanation may be, it is nevertheless interesting to note that the animal showing the more profound renal functional and morphologic changes excreted less salicylate than the animal with the less pronounced changes. This coincides with certain observations reported by Hanzlik, Scott and Thoburn[9] on the excretion of salicylate in human beings with different clinical conditions as compared with normal individuals.

CONCLUSIONS

1. The administration of salicylate in doses corresponding to full therapeutic doses for human beings per kilo of body weight, causes the appearance of albumin, leukocytes, casts or cast-like bodies, and sometimes red blood corpuscles, in the urine of animals (cats, dogs and one rabbit).

2. A pre-existing albuminuria is aggravated by the administration of salicylate.

3. The albuminuria is of direct renal origin.

4. So far as the nonprotein and urea nitrogen of the blood are concerned, there is a diminution in renal functional efficiency.

5. Morphologically, a lesion of the kidney appears, varying in severity from simple cloudy swelling of the epithelium of the proximal convoluted tubule to extensive cloudy swelling of all the cortical parts of the tubules, associated with an acute intracapillary glomerulitis, the latter process being denominated as an acute tubular nephritis.

PROTOCOLS

EXPERIMENT 1.—Dog; 3.1 kg. Urine before salicylate was albumin-free; received 0.3 gm. sodium salicylate per kilo by mouth; 1 hour later there was marked albuminuria. On the following day there was still marked albuminuria; received two doses of 0.3 gm. each per kilo, but vomited almost immediately after each dose; 4 gm. of salicylate were then injected in three divided doses

9. Hanzlik, P. J., Scott, R. W., and Thoburn, T. W.: The Salicylates. V. Secretion of Salicyl in the Urines of Rheumatic and Non-Rheumatic Individuals, Jour. Pharm. and Exper. Therap., 1917, **9**, 247.

hypodermically within thirty minutes; animal was killed 1¼ hours after last dose. Albuminuria was severe; red and white cells were present in the urine.

Histologically the glomeruli show slight congestion, but otherwise normal tufts; occasional glomeruli show albuminous precipitate in the subcapsular space. Epithelium of the proximal convoluted tubules shows moderate cloudy swelling; the lumina of these tubules are normal. There are no casts.

Diagnosis: Cloudy swelling of kidney.

EXPERIMENT 2.—Dog; 5.4 kg. Urine before salicylate contained traces of albumin, which was markedly increased, together with the appearance of white and red cells after the subcutaneous injection of 0.9 gm. sodium salicylate. Two days later the animal received 3.3 gm. salicylate in two divided doses. The animal died during the night; urine from bladder gave strong albumin tests and showed the presence of white and red corpuscles.

Histologic picture somewhat obscured by postmortem degeneration. Glomerular tufts normal save for slight congestion; the subcapsular spaces contain much granular precipitate and also a moderate number of desquamated capsular epithelial cells; this latter condition, however, is probably the result of postmortem changes. The epithelium of the convoluted tubules shows marked granularity and the lumina contain many albuminous granules. There are no casts. Other tubules show less marked granular change. Around some of the large blood vessels there is an old connective tissue growth.

Diagnosis: Postmortem degeneration and probably cloudy swelling of kidney.

EXPERIMENT 3.—Dog; 5.6 kg. For four days previous to injection of salicylate, the urine showed a trace of albumin. On day of experiment the urine was albumin-free. Received single injection of 0.05 gm. salicylate per kilo hypodermically. Seven hours later the urine gave strong albumin tests and showed the presence of white and red corpuscles; dog found dead in cage next morning; 5 c.c. of urine obtained from the bladder; this gave strong albumin tests, and showed numerous white corpuscles and granular cast-like bodies.

Postmortem degeneration has advanced to such a degree as to render histologic description useless.

EXPERIMENT 4.—Cat; 3.2 kg. Urine before salicylate showed questionable trace of albumin for two days; 1.05 gm. sodium salicylate was injected in three divided doses in the course of forty-five hours; 700 c.c. water were administered at different times and about 300 c.c. urine were voided during this interval. The animal was killed. The urine at all times gave marked albumin tests and showed many white, and a few red corpuscles.

Histologically the glomeruli show practically normal vascular tufts; the subcapsular space in many instances shows a moderate amount of albuminous precipitate; a small number of glomeruli show swelling of the capsular epithelium. The epithelium of the proximal convoluted tubules show well marked granularity of the protoplasm, in some instances hyaline droplet formation, and infrequently many desquamated epithelial cells. The tubules otherwise are normal; there are no casts.

Diagnosis: Cloudy swelling of kidney. The change might be called by some authors an acute tubular nephritis, but without more marked tubular change, and especially in the absence of notable change in the glomerular tuft, such a diagnosis seems hardly justifiable.

EXPERIMENT 5.—Cat; 3 kg. Trace of albumin present in urine for a week before salicylate; 0.9 gm. sodium salicylate injected in two successive days; total injected 1.8 gm. Following second injection, marked albuminuria, few granular casts; many leukocytes, few erythrocytes; animal was killed in a dying condition on the second day.

Histologically the interstitial tissue is normal. The glomeruli show normal capsules and no exudate in the subcapsular space, but the vascular tufts are large, fill the capsular spaces and are almost devoid of blood. The epithelium

of the cortical tubules contains much fat, but marked granularity of the protoplasm can easily be made out, and the lumina of many of the tubules contain fine and coarsely granular albuminous precipitate.

Diagnosis: Acute tubular nephritis.

EXPERIMENT 6.—Cat; 2.1 kg. Trace of albumin in urine before salicylate; 0.6 gm. sodium salicylate injected in two doses within twenty-six hours; total injected 1.2 gm. Marked albuminuria together with granular casts and leukocytes. Animal markedly depressed; killed.

Histologically, the interstitial tissue and the glomeruli are in all respects normal. The epithelium of proximal and distal convoluted tubules, as well as of the ascending loop of Henle, show various stages of cloudy swelling, from swelling of the epithelium with occlusion of the lumen to narrowing of the epithelial lining, with the presence of a considerable amount of granular precipitate in the lumina. There are a few hyaline casts and a few minute interstitial hemorrhages.

Diagnosis: Slight cloudy swelling; almost a normal kidney.

EXPERIMENT 7.—Rabbit; 1.2 kg. Urine free from albumin before salicylate; 2.2 gm. sodium salicylate injected in four doses on three successive days. Following each injection, mild albuminuria, together with occasional granular and hyaline casts. Throughout the experiment the animal appeared normal; killed.

Histologically, the interstitial tissue shows numerous small areas of overgrowth with associated atrophy of tubules and glomeruli. In the large areas between these foci the interstitial tissue is apparently normal. The glomerular capsules and subcapsular spaces show nothing pathologic. The vascular tufts are large, bloodless and apparently the seat of an acute glomerulitis. In somewhat irregularly distributed areas the convoluted tubules show marked granularity, vagueness of outline, fragmentation and desquamation, with slight pyknosis of a few of the nuclei. The tubular lumina contain granular albuminous precipitate and a few hyaline casts.

Diagnosis: Acute tubular nephritis superimposed on chronic interstitial nephritis.

EXPERIMENT 8.—Cat; 1.9 kg. Slight albuminuria present before salicylate. A single injection of 0.6 gm. sodium salicylate was given. Animal found dead in cage next morning; bladder urine contained large quantity of albumin and casts.

Histologically, the interstitial tissue and the glomeruli are normal, except that a very few of the latter show large, bloodless, richly cellular, vascular tufts. The epithelium of the cortical tubules is more granular than normal and occupies a decreased space in the tubule. The correspondingly enlarged lumina are filled with finely and coarsely granular albuminous precipitate. Several arched collecting tubules contain hyaline casts.

Diagnosis: Acute tubular nephritis.

EXPERIMENT 9.—Cat; 1.3 kg. Trace of albumin in urine before salicylate; 0.85 gm. sodium salicylate injected in two doses on two successive days. Animal died in 1½ hours after second injection; kidneys excised immediately after death; bladder urine gave strong tests for albumin; granular casts present.

Histologically, the interstitial tissue is normal, as are also the glomerular capsules and subcapsular spaces. The glomerular tufts are large, devoid of blood and richly cellular. The epithelium throughout the cortex shows cloudy swelling, but in the proximal and distal convoluted tubules the granulation is very marked; there is fragmentation and desquamation of cells, the tubular lumina are filled with albuminous precipitate and an occasional narrow hyaline cast can be seen.

Diagnosis: Acute tubular nephritis.

EXPERIMENT 10.—Dog; 6.5 kg. Urine free from albumin and casts before salicylate; 6.05 gm. sodium salicylate injected in four divided doses on four

TABLE SHOWING EFFECT OF SALICYLATE ON KIDNEY[1]

Number and Animal	Body Weight, Kg.	Total Quantity of Sod. Salicylate[2] Administered, Gm.	No. of Toxic Doses	Mode of Administration	Albuminuria		N.P.N. and Urea-N in Blood (Mg. in 100 C.c.)		Reaction of Blood (pH) and Alkali Reserve (RpH)		Pathologic Diagnosis	Experiment Terminated End of
					B. S.	A. T.	B. S.	A. T.	B. S.	A. T.		
Dog 1	3.1	4.6	6	Hypo + per os	+st	+st	.....	.....	.....	.....	Cloudy swelling	2 days
Dog 2	5.4	4.2	3	Hypo.	+tr	+st	.....	.....	.....	.....	Cloudy swelling (?)	3 days
Dog 3	5.6	0.05	1	Hypo.	—	+	N.P.N. 52.0	62.0	.....	.....	.....	2 days
Cat 4	3.2	1.05	3	Hypo.	+?	+	N.P.N. 22.4	130.4	.....	.....	Cloudy swelling	45 hours
Cat 5	3.0	1.8	2	Hypo.	+tr	+	.....	.....	.....	.....	Acute tubular nephritis	3 days
Cat 6	2.1	1.2	2	Hypo.	+sl	+st	.....	.....	.....	.....	Very slight cloudy swelling	26 hours
Rabbit 7	1.2	2.2	4	Hypo.	+sl	+st casts	.....	.....	.....	.....	Acute tubular nephritis superimposed on chronic interstitial nephritis	3 days
Cat 8	1.9	0.6	1	Hypo.	+sl	+st	.....	.....	.....	.....	Acute tubular nephritis	20 hours (?) (Died during night)
Cat 9	1.2	0.85	2	Hypo.	+sl	+st	.....	.....	pH 7.4	pH 7.4	Acute tubular nephritis	20 hours
Dog 10	6.5	6.05	4	Hypo.	—	+	N.P.N. 20.0	(1) 40.2 (2) 49.0 (3) 66.7 (4) 80.0	.....	.....	(No sections)	4 days

Dog 11	6.3	2.19	3	Hypo.	+sl	+	Urea N 24.5	(1) 24.2 (2) 18.0 (3) 40.3	pH 7.6	pH 7.7 7.6 7.6	Cloudy swelling	3 days
Dog 12	5.5	3.5	2	Hypo.	+vsl	+	Urea N 6.03	(1) 6.2 (2) 8.73 (3) 18.2	pH 7.7	pH 8.0	Cloudy swelling	3 days
Cat 13	2.1	0.94	1	Hypo.	+	+	Urea N 20.4	20.3	pH 7.6 RpH 8.2	pH 7.6 RpH 8.2	Acute tubular nephritis	26 hours
Cat 14	0.5	0.15	1	Hypo.	No urine	No urine	Urea N 12.8	13.7	.....	.....	Acute tubular nephritis	6½ hours
Cat 15	0.5	0.15	1	Hypo.	No urine	No urine	Urea N 16.1	.....	.....	.....	Slight cloudy swelling	6½ hours
Cat 16	2.0	0.6	1	Hypo.	+sl	+ casts	Urea N 20.1	25.8	.....	.....	Acute tubular nephritis	9 hours
Dog 17	7.5	3.0	2	Per os	+	+	Urea N 8.56	(1) 4.1 (2) 3.3 (3) 6.2 (4) 12.3 (5) 12.8 (6) 18.0 (7) 18.2 (8) 19.3 (9) 14.0	pH 7.8 RpH 8.4	pH 7.7 RpH 8.2 7.8 8.2 7.8 8.2 7.5 8.5 7.7 8.4 7.6 8.2 7.6 8.4 7.6 8.6 7.6 8.4	Acute tubular nephritis	9 days
Dog 18[3]	4.0	1.2	1	Hypo.	+	+	Urea N 7.1	(1) 12.8 (2) 12.8 (3) 16.0 (4) 18.6	.....	.....	Acute tubular nephritis	4 days
Dog 19[4]	5.8	1.3	1	Hypo.	—	+	Urea N 11.0	(1) 14.0 (2) 14.1 (3) 9.5 (4) 10.0	.....	.....	Marked cloudy swelling	4 days

1. The abbreviations in the table have meanings as follows: B. S. = before salicylate; A. T. = at "toxicity"; or when the effects of the salicylate were evident as indicated by symptoms of nausea, vomiting, loss of equilibrium, etc.; N.P.N. = nonprotein nitrogen; pH = hydrogen-ion concentration; RpH = reserve alkalinity; st = strong; sl = slight; + = present; — = absent; figures in parentheses refer to days.

2. Sodium salicylate contains 86 per cent. salicylic acid.

3. Total quantity of salicyl recovered in urine = 26.6 per cent. The distillation-colorimetric method was used as described by Thoburn and Hanzlik: Jour. Biol. Chem., 1915, 23, 163.

4. Total quantity of salicyl recovered in urine = 55.4 per cent.

successive days. Within one to two hours after each of the first two injections the dog was depressed, with increased respiration. On the day of the third injection the animal appeared normal and in good condition, but following the third and fourth injections of the drug the animal became progressively more depressed and weak and died sometime during the following night and day (over Sunday). Albuminuria, together with leukocytes and considerable epithelium, appeared following the first injection and progressively increased until death (at times red corpuscles were present). Kidneys not sectioned because of postmortem changes.

EXPERIMENT 11.—Dog; 6.3 kg. Mild albuminuria together with leukocytes present before salicylate. Sodium salicylate was injected in three divided doses on three successive days as follows; 0.3 gm. daily for the first two days, and 1.89 gm. on the third day; total injected, 2.19 gm. Dog vomited and showed considerable depression after each injection. Albuminuria, together with casts, leukocytes and epithelium, progressively increased until the animal was killed on the third day. Blood was obtained from the heart daily for urea nitrogen determination; pericardium and myocardium appeared normal.

Histologically, the interstitial tissue and glomeruli are normal. The cortical tubules show a narrowed epithelial lining, the cells of which show increased granularity and fragmented, ragged edges; the tubular lumina are well filled with granular albuminous precipitate.

Diagnosis: Cloudy swelling.

EXPERIMENT 12.—Dog; 5.5 kg. Faint trace of albumin in urine before salicylate; 3.5 gm. sodium salicylate injected in two doses on successive days. Considerable depression and vomiting followed second injection. Marked albuminuria, together with granular casts, leukocytes, some erythrocytes and clumps of epithelium present in urine. Animal killed.

Histologically, the interstitial tissue is normal, as also are the glomeruli, except for a slight deposit of granular albuminous material in the subcapsular space. The epithelium of the cortical tubules is more granular than normal and the tubular lumina, increased in caliber, contain much albuminous granular precipitate.

Diagnosis: Cloudy swelling.

EXPERIMENT 13.—Cat; 2.1 kg. Albuminuria present before salicylate; 0.94 gm. sodium salicylate injected as follows: 0.62 gm. on the first day, 0.32 gm. on the second day. Convulsions of medullary type occurred about eight hours after first injection, and cat died in about two hours after the second injection. Albumin in urine present after each injection, though not marked.

Histologically, the interstitial tissue is normal. The glomerular tufts are large, richly cellular and bloodless. The convoluted tubules show a moderate amount of fat. The cortical tubules as a whole show marked granularity of cell protoplasm, in several places, desquamation. The tubular lumina contain albuminous granular material and several of the distal convoluted tubules show an accumulation of hyaline material in the lumina, not as yet fused and separated to form casts.

Diagnosis: Acute tubular nephritis.

EXPERIMENT 14.—Kitten; 0.5 kg. No urine obtainable at any time. Single dose of 0.15 gm. sodium salicylate injected. Animal remained in good condition; killed at the end of 6½ hours after injection.

The histologic changes in this kidney are practically the same as those seen in Animal 13.

Diagnosis: Acute tubular nephritis.

EXPERIMENT 15.—Kitten; 0.5 kg. No urine obtainable at any time. Single dose of 0.15 gm. sodium salicylate injected. Considerable depression at the end of six hours after injection; died while attempting to secure blood from heart.

Histologically, the interstitial tissue is normal. The glomeruli are large, contain a moderate amount of blood and there is a small amount of granular albuminous precipitate in the subcapsular spaces.

The cortical tubular epithelium shows slightly increased granularity and the tubular lumina contain a small amount of granular albuminous material.

Diagnosis: Slight cloudy swelling.

EXPERIMENT 16.—Cat; 2 kg. Slight albuminuria, together with leukocytes before salicylate. Single dose of 0.6 gm. sodium salicylate injected. Albuminuria considerably increased; leukocytes numerous; some erythrocytes and cast-like bodies. Animal killed at end of nine hours after injection.

Histologically, the interstitial tissue is normal. The vascular tufts of the glomeruli are large, contain an occasional erythrocyte, but are more richly cellular than normal and frequently show filling of capillary loops by endothelium. The subcapsular spaces contain albuminous granular precipitate. The cortical tubules show well-marked cloudy swelling, most marked in the proximal convoluted tubules, where the cells are large and extremely granular, and the tubular lumina are filled with much albuminous granular precipitate.

Diagnosis: Acute tubular nephritis.

EXPERIMENT 17.—Dog; 7.5 kg. Albuminuria present, but no casts before salicylate. On the first day 0.25 gm. sodium salicylate was administered into the stomach every hour until six doses were given; total salicylate administered, 1.5 gm. Urine was expressed from the bladder at intervals, but contained no more albumin than before salicylate; no casts; occasional leukocytes and erythrocytes present; no vomiting; no depression. On the second day 1.5 gm. salicylate were administered in the same way as on the first day; total salicylate administered in experiment, 3 gm. Vomiting occurred after the last dose was administered; the animal showed some depression and incoordination; more vomiting occurred during the following night. The animal was observed continuously for seven days after the last injection; total observation period, nine days. Albuminuria increased gradually up to the fourth day after injection of salicylate, then gradually diminished until the last day, when only a fairly positive trace of albumin was present; no casts at any time. The animal gained weight slightly (160 gm.) and remained in good condition throughout the experiment. Blood from the heart was obtained daily for urea nitrogen and reaction estimations; killed on the ninth day.

Histologically, the interstitial tissue is normal. The vascular tufts of the glomeruli are large, bloodless and richly cellular. The subcapsular spaces contain granular albuminous precipitate. The cortical tubules show cloudy swelling, most markedly in the proximal convoluted tubules, where there is marked granularity of the epithelium as well as fragmentation and desquamation. The tubular lumina show much granular albuminous material and a few epithelial and coarsely granular casts.

Diagnosis: Acute tubular nephritis.

EXPERIMENT 18.—Dog; 4 kg. Albumin present (more than a trace) and some leukocytes before salicylate. A single dose of 1.2 gm. sodium salicylate (actually 1.32 gm. salicylic acid) was injected hypodermically. Animal observed for next four days. Dog originally was not very vigorous; no depression from salicylate, but progressively became morose, emaciated and emitted a foul odor from the oral cavity, which showed signs of infection; site of salicylate injection was edematous and necrotic. Albuminuria, together with leukocytes, present throughout experiment, and remained about the same after the salicylate. Blood was secured from the heart daily for urea nitrogen estimation; killed on fourth day. Pericardium and myocardium appeared normal. Left kidney showed about ten large, irregular white patches diffusely scattered on the surface; in some places these appeared to be raised, resembling miliary tubercles. The right kidney showed three such patches. Other viscera appeared normal. The

total quantity of salicylate recovered from the cage contents (urine, etc.) was 26.6 per cent., expressed as salicylic acid.

Histologically, the interstitial tissue is normal. The glomeruli show large, bloodless, richly cellular vascular tufts and a small amount of finely granular albuminous precipitate in the subcapsular space. The cortical tubular epithelium shows cloudy swelling, most markedly in the proximal convoluted tubules, where there is marked granularity, fragmentation and desquamation, the tubular lumina containing granular albuminous material but no casts.

Diagnosis: Acute tubular nephritis.

EXPERIMENT 19.—Dog; 5.8 kg. Urine practically free from albumin before salicylate. Single dose of 1.3 gm. sodium salicylate (actually 1.235 gm. salicylic acid). Animal became nauseated, but no vomiting occurred; for two days following the injection, the albuminuria increased, then gradually disappeared, only a trace being present on the last day of the experiment. Blood was secured daily from the heart for urea nitrogen estimation; the animal remained in good condition; killed on the fourth day; all viscera appeared normal. The total quantity of salicylate recovered from the cage contents (urine, etc.) was 55.4 per cent., expressed as salicylic acid.

Histologically, the interstitial tissue is normal. The glomeruli are normal, except that the subcapsular spaces frequently contain granular albuminous precipitate. The cortical tubular epithelium, as in Dog 18, shows cloudy swelling, most markedly in the proximal convoluted tubules where there is marked granularity, fragmentation and desquamation, the tubular lumina containing granular albuminous material but no casts.

Diagnosis: Marked cloudy swelling.

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THE SALICYLATES

VII. FURTHER OBSERVATIONS ON ALBUMINURIA AND RENAL FUNCTIONAL CHANGES FOLLOWING THE ADMINISTRATION OF FULL THERAPEUTIC DOSES OF SALICYLATE *

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In a previous communication[1] it was shown that the administration of salicylate in full therapeutic doses invariably causes the appearance of albumin, together with leukocytes and casts or cast-like bodies, in the urines of rheumatic and nonrheumatic individuals. The observations on renal function were inconclusive because of the variations and small differences in both the phenolsulphonephthalein excretion and nonprotein nitrogen of the blood before and after the administration of the drug. It was definitely shown, however, that the albuminuria is not of febrile, but of direct renal origin. The albuminuria, in some cases, is so severe that the presence of a nephritis is suggested. This was found to be the case in animals[2] (cats, dogs and a rabbit) receiving quantities of salicylate per kilo of body weight corresponding to the full therapeutic dose in human beings, in single and repeated doses, by mouth and subcutaneously. The pathologic changes in the kidney were interpreted as an acute tubular nephritis. An accumulation of nonprotein and urea nitrogen in the bloods of a majority of the animals was also demonstrable. In other words, salicylate, in these animals, caused a diminution in renal functional efficiency, so far as these tests are concerned.

These findings encouraged us to extend our former observations, and arrive, if possible, at some final decision concerning the effects of salicylate on renal function in human beings. If it could be definitely shown that the drug injures the kidney, it should engender caution in its careless or promiscuous use as a remedy, particularly as to repeated administrations.

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1. Scott, R. W., and Hanzlik, P. J.: Jour. Am. Med. Assn., 1916, **67,** 1838.
2. Hanzlik, P. J., and Karsner, H. T.: THE ARCHIVES INT. MED., this issue, p. 1016.

TABLE 1.—Clinical Data *

Number and Patient	Diagnosis	Condition of Temperature	Fluid Intake	Toxic Dose of Salicyl,† Gm.	Diaphoresis	Urinary Changes						Administered Sodium Bicarbonate Together With Salicyl, Gm.
						Albumin		White Blood Corpuscles		Granular Casts or Castlike Bodies		
						Before Salicyl	During Salicyl Medication	Before Salicyl	During Salicyl Medication	Before Salicyl	During Salicyl Medication	
1 (P. F.)‡	Rheumatic fever	Febrile	250 c.c. every hour for 12 hrs.; 250 c.c. every 2 hrs. thereafter	13.41	Moderate	—	+					
2 (J. M.)	Rheumatic fever	Febrile	170 c.c. every hour for 8 hrs.; 300 c.c. every 2 hrs. thereafter	12.81	Profuse	—	+	—	+	—	+	
3 (W. C.)	Rheumatic fever	Febrile	100 c.c. every hour for 9 hrs.; 200 c.c. every 2 hrs. thereafter	15.48	Profuse	+ tr.	+ inc.	+ oc.	+ inc.	+ oc.	+ inc.	
4 (J. H.)‡	Rheumatic fever	Febrile	230 c.c. every hour for 8 hrs.; 400 c.c. every 2 hrs. thereafter	14.45	Profuse	+	+ inc.	—	+	—	+	
5 (J. L.)‡	Rheumatic fever	Febrile	200 c.c. every hour for 8 hrs.; 400 c.c. every 2 hrs. thereafter	14.45	Very profuse	+ tr.	+ inc.	+ oc.	+ inc.	—	+ oc.	
6 (F. D.)	Appendicitis T. B. kidney (?)	Afebrile	180 c.c. every hour for 7 hrs.; 300 c.c. every 2 hrs. thereafter	12.04	Mild	+ tr.	+ inc.	+ oc.	+ inc.	—	+	
7 (L. E.)	Tabes	Afebrile	150 c.c. every hour for 8 hrs.; 300 c.c. every 2 hrs. thereafter	13.76	Marked	+ tr.	+ inc.	+ oc.	+ inc.	—	+	
8 (H. M.)	Normal	Afebrile	150 c.c. every hour for 9 hrs.; 400 c.c. every 2 hrs. thereafter	15.48	Mild	—	+	+ oc.	+ inc.	—	+	
9 (A. P.)	Normal	Afebrile	100 c.c. every hour for 12 hrs.; 200 c.c. every 2 hrs. thereafter	14.96	Very mild	—	+	—	+	—	+	
10 (J. B.)	Normal	Afebrile	100 c.c. every hour for 11 hrs.; 200 c.c. every 2 hrs. thereafter	19.30	.....	+ tr.	+ inc.	—	+	—	+	
11 (S. V.)	Rheumatic fever	Febrile	100 c.c. every hour for 11 hrs.; 200 c.c. every 2 hrs. thereafter	18.33	Moderate	+ tr.	+ inc.	+ oc.	+ inc.	+	+ inc.	
12 (W. B.)	Rheumatic fever Old T. B. lesion of apex	..... Febrile	100 c.c. every hour for 5 hrs.; 200 c.c. every 2 hrs. thereafter	8.75	Very profuse	+ tr.	+ inc.	—	+	—	+	
13 (D. T.)‡	Normal	Afebrile	100 c.c. every hour for 7 hrs.; 200 c.c. every 2 hrs. thereafter	13.3	Mild	+ tr.	+ inc.	—	+	—	—	14.0
14 (J. T.)‡	Normal	Afebrile	100 c.c. every hour for 6 hrs.	10.5	Mild	+ tr.	+ inc.	+ oc.	+ inc.	—	—	
15 (M. Z.)‡	Normal	Febrile	100 c.c. every hour for 6 hrs.	10.5	Marked	+ st.	+ inc.	+	+ inc.	+	+	

16a (M. C.)‡	Lessened renal functional efficiency; hysteria	Afebrile	100 c.c. every hour for 6 hrs.; 200 c.c. every 2 hrs. thereafter	12.3	Mild	+ tr.	+ inc.	+ oc.	+ inc.	+ oc.	+ inc.	
16b (M. C.)‡	Lessened renal functional efficiency; hysteria	Afebrile	100 c.c. every hour for 6 hrs.; 200 c.c. every 2 hrs. thereafter	11.4	Mild	+ tr.	+ inc.	+ oc.	+ inc.	+ oc.	+ inc.	12.0
16c (M. C.)‡	Lessened renal functional efficiency; hysteria	Afebrile	100 c.c. every hour for 7 hrs.; 200 c.c. every 2 hrs. thereafter	10.5	Mild	+	+ inc.	+ oc.	+ inc.	+ oc.	+ inc.	
16d (M. C.)‡	Lessened renal functional efficiency; hysteria	Afebrile	100 c.c. every hour for 6 hrs.; 200 c.c. every 2 hrs. thereafter	9.86	Mild	+ tr.	+ inc.	+ oc.	+ inc.	+ oc.	+ inc.	
17 (P. K.)	Chronic alcoholism	§	100 c.c. every hour for 7 hrs.; 200 c.c. every 2 hrs. thereafter	12.3	Mild	+	+ inc.	+ oc.	+ inc.	+ oc.	+ inc.	14.0
18 (F. S.)	Chronic alcoholism	Afebrile	100 c.c. every hour for 6 hrs.; 200 c.c. every 2 hrs. thereafter	10.8	Profuse	+	+ inc.	+	+ inc.	+	+ inc.	
19 (Y. V.)	Tuberculosis	Very febrile	100 c.c. every hour for 6 hrs.; 200 c.c. every 2 hrs. thereafter	10.8	Moderate	+	+ inc.	+	+ inc.	+	+ inc.	
20 (G. W.)	Chronic morphinism	Afebrile	100 c.c. every hour for 6 hrs.; 200 c.c. every 2 hrs. thereafter	10.9	Mild	+ tr.	+ inc.	+	+ inc.	+	+	
21a (J. V.)	Rheumatic fever	Febrile	100 c.c. every hour for 6 hrs.; 200 c.c. every 2 hrs. thereafter	10.2	Profuse	+	+ inc.	+	+ inc.	+	+	
21b (J. V.)	Normal	Afebrile	100 c.c. every hour for 5 hrs.; 200 c.c. every 2 hrs. thereafter	9.5	Mild	—	+ inc.	—	+	—	—	
22 (E. L.)	Surg. (?)¶	Afebrile	100 c.c. every hour for 5 hrs.; 200 c.c. every 2 hrs. thereafter	9.0	Mild	+ tr.	+ inc.	—	+	—	+	
23 (E.)	Chronic rheumatism	Afebrile	100 c.c. every hour for 5 hrs.; 200 c.c. every 2 hrs. thereafter	9.5	Marked	+	+ inc.	+	+ inc.	+	+ inc.	
24 (J. H.)	Endocarditis; cardiac decompensation	Afebrile	100 c.c. every hour for 5 hrs.; 200 c.c. every 2 hrs. thereafter	8.1	Mild	+	+ inc.	+	+ inc.	+	+ inc.	
25 (H. V.)	Normal; photophobia	Afebrile	100 c.c. every hour for 5 hrs.; 200 c.c. every 2 hrs. thereafter	9.0	Mild	—	+	—	+	—	—	
26 (R. H.)	Normal; ulcer of eye	Afebrile	100 c.c. every hour for 7 hrs.; 200 c.c. every 2 hrs. thereafter	12.6	Marked	+	+ inc.	+	+ inc.	+ oc.	+	
27 (J. M.)	Normal; varicose ulcer	Afebrile	100 c.c. every hour for 7 hrs.; 200 c.c. every 2 hrs. thereafter	12.6	Mild	+	+ inc.	+	+	+ oc.	+	14.0
28 (T. S.)	Normal	Afebrile	100 c.c. every hour for 5 hrs.; 200 c.c. every 2 hrs. thereafter	9.0	Very mild	—	+	—	+	—	+ oc.	9.0

* In this table the various signs and abbreviations have meanings as follows: plus (+) sign, present; minus (—) sign, absent; tr., trace; inc., increased; oc., occasional; st., strong

† Salicyl was administered in form of sodium salicylate, expressed as salicylic acid.

‡ The albuminuria in this individual was not studied quantitatively. In such cases, the urines were either utilized for other quantitative studies, or they had stood too long to give trustworthy results for albumin.

§ Partially febrile, temperature reaching a maximum of 99.8 F.

¶ A surgical condition, possibly renal; diagnosis incomplete.

It is the object of this paper to summarize the results of all of our observations on the effects on human renal functional efficiency. Observations on twelve additional individuals have been added to the sixteen previously reported, making a total, therefore, of twenty-eight different individuals, and thirty-two observations. A definite quantity (20 c.c.) of salicyl (usually of about 10 per cent. strength) in the form of sodium salicylate was administered, together with 80 c.c. of water, every hour until the subject complained of the well known symptoms of "toxicity." Then the administration was stopped, but the water was continued, usually 200 c.c. every two hours, until the excretion of salicyl in the urine ceased. That is, the fluid intake was maintained constant throughout as nearly as possible. Urine was collected every ten hours throughout the experiment and examined qualitatively (by the heat and acetic acid and ferrocyanid tests), and quantitatively (by the gravimetric method of Folin and Denis) for the presence of albumin, and microscopically for leukocytes, casts, etc., before and after the administration of the drug. Other tests of renal functional efficiency (before and after the administration of salicyl) were made as follows: The total nonprotein nitrogen of the blood was estimated according to the method of Folin and Denis,[3] using titration and distillation instead of the colorimetric procedure. The urea nitrogen content of the blood was estimated by the urease, aeration and colorimetric procedure.[4] The percentage excretion of phenolsulphonephthalein in two hours was studied in the usual way. The various clinical data pertaining to all the subjects are summarized in Table 1.

1. *Salicyl Causes Albuminuria and Aggravates a Pre-existing Albuminuria.*—In all the individuals of the present series, the administration of salicylate was followed by the presence of albumin, leukocytes and granular casts or cast-like bodies in their urines. This is, therefore, confirmative of our former observations. It is further confirmed that the albuminuria is not of febrile, but of direct renal origin, for it occurs in febrile, afebrile, rheumatic, nonrheumatic and normal persons.

Many of the individuals showed some degree of albuminuria before the drug was administered. It was, therefore, necessary to study the excretion quantitatively in order to ascertain definitely if this was increased by the salicylate. This was done by the gravimetric method of Folin and Denis.[5] The results from all the individuals studied (twenty-two) are presented in Table 2, and in Figure 1, which presents

3. Folin and Denis: Jour. Biol. Chem., 1912, **11,** 527.

4. We wish to express our thanks to Dr. Cyrus H. Fiske of the Biochemical Laboratory for suggesting the use of a glycerin extract of the jack bean for the urease.

5. Folin and Denis: Jour. Biol. Chem., 1914, **18,** 273.

TABLE 2.—EXCRETION OF ALBUMIN IN URINE OF INDIVIDUALS RECEIVING FULL THERAPEUTIC DOSES OF SALICYLATE

No.	Grams of Albumin Excreted in Each Ten-Hour Period									
	B. S.*	1	2	3	4	5	6	7	8	9
2	0.0	0.43	0.14	0.09	0.05	0.11	0.0	0.0	0.0	0.0
3	0.0	0.12	0.48	0.41	0.32	0.31	0.18	0.0	0.0	0.0
6	0.0	0.13	0.07	0.16	0.42	0.10	0.37	0.09	0.03	0.0
7	0.0	0.16	0.06	0.03	0.02	0.01	0.0	0.0	0.0	0.0
8	0.0	0.32	0.03	0.27	0.14	0.02	0.49	0.0	0.0	0.0
9	0.0	0.0	0.0	0.05	0.08	0.03	0.01	0.01	0.0	0.0
10	0.21	0.69	0.43	0.66	0.70	0.72	0.60	0.22	0.29	0.11
11	0.10	0.13	0.18	0.11	0.25	0.18	0.16	0.04	0.06	0.04
12	0.09	0.29	0.10	0.04	0.10	0.04	0.07	0.18	0.10	0.10
16b†	0.003	0.03	0.21	0.09	0.07	0.03	0.01	0.02	0.08	0.04
16c	0.05	0.01	0.10	0.06	0.05	0.15	0.08	0.02	0.06	0.006
16d	0.002	0.01	0.10	0.02	0.12	0.06	....	0.07	0.0	0.0
17†	0.04	0.20	0.05	0.24	0.06	0.10	0.06	0.02	0.03	0.14
18	0.11	0.16	0.13	0.05	0.08	0.03	0.09	0.05	0.03	0.04
19	0.06	0.19	0.27	0.47	0.42	0.25	0.31	0.38	0.003	0.13
20	0.01	0.38	0.28	0.02	0.006	0.02	0.07	0.05	0.05	0.02
21a	0.22	0.32	0.55	0.48	1.17	0.16	0.01	....	....	0.13
22	0.06	0.05	0.09	0.04	0.05	0.04	0.02	0.01	0.03	0.0
21b	0.0	0.04	0.13	0.06	0.02	0.0	0.0	0.0	0.0	0.0
23	0.02	0.07	0.08	0.03	0.01	0.09	0.11	0.0	0.26	0.08
24	0.0	0.06	0.31	0.22	0.23	0.24	0.05	0.08	....	0.04
25	0.0	0.06	0.09	0.12	0.14	0.08	0.06	0.02	0.0	0.0
26	0.05	0.28	0.12	0.12	0.46	1.98	0.58	0.21	0.0	0.0
27†	0.04	0.18	0.38	0.35	0.06	0.02	0.09	0.05	0.0	0.0
28†	0.0	0.09	0.03	0.04	0.02	0.07	0.05	0.02	0.0	0.0
Median	0.02	0.13	0.13	0.10	0.08	0.09	0.07	0.02	0.02	0.03

* B. S. means "before salicyl."
† Received bicarbonate together with salicylate.

the course of the excretion by a curve of median values. This shows conclusively that a pre-existing albuminuria is aggravated by the administration of salicyl. It will be seen, also, that the albuminuria reaches its maximum at, or shortly after, "toxicity," and gradually tends to reach its previous level. As judged from the estimations of the salicyl content of these urines, the cessation of albumin excretion roughly coincides with the cessation of salicyl excretion. In a number of the individuals, however, the albuminuria tended to persist.

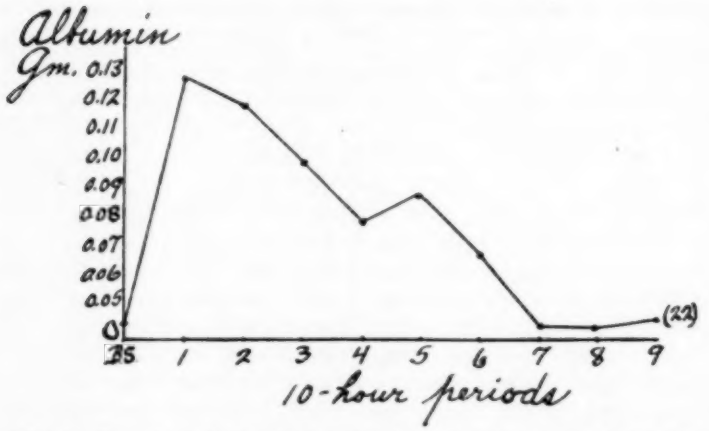

Fig. 1.—Excretion of albumin in urine in each ten-hour period following the administration of full therapeutic doses of salicylate. The curve represents median values; the number in parenthesis refers to number of different individuals; B. S. means "before salicyl."

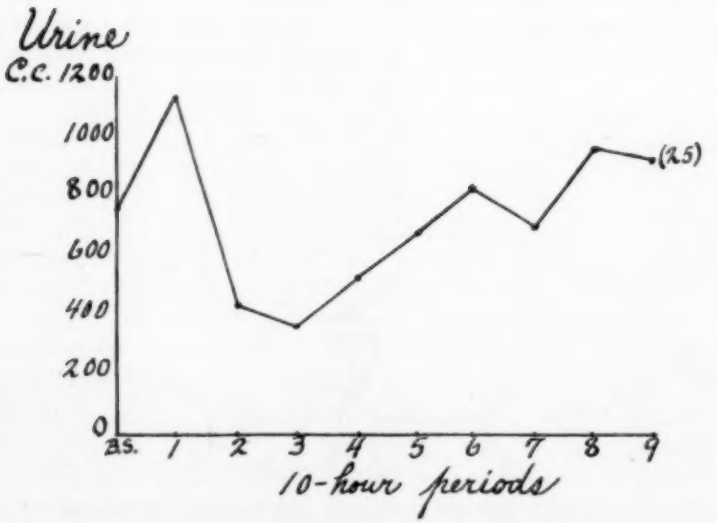

Fig. 2.—Excretion of urine in each ten-hour period following the administration of full therapeutic doses of salicylate. The curve represents median values; the number in parenthesis refers to number of different individuals; B. S. means "before salicyl."

TABLE 3.—EXCRETION OF URINE BY INDIVIDUALS RECEIVING FULL THERAPEUTIC DOSES OF SALICYLATE

No.	C.c. of Urine Excreted in Each Ten-Hour Period										
	B. S.*	1	2	3	4	5	6	7	8	9	10
1	....	1,720	1,123	708	428	404	1,060	1,858			
2	....	1,768	2,322	754	814	1,504	1,606	1,840	1,433		
3	....	2,001	446	320	274	343	325	638	943	864	791
4	....	2,153	1,094	1,307	1,884	1,586	1,586	2,080	1,642	2,144	2,073
5	....	1,074	714	579	634	400	662	464	1,491	1,191	928
6	....	3,239	469	1,315	899	1,071	978	708	670		
7	....	1,405	1,399	925	1,092	1,333	1,088	875	1,206	502	
8	....	1,970	786	1,359	1,549	1,695	1,478	1,562	2,264		
9	....	810	550	625	230	360	185	690	755	1,027	
10	....	855	210	425	530	840	810	460	550	350	1,275
11	....	595	420	175	495	290	263	455	375	387	392
12	....	640	340	660	680	690	1,130	776	1,420	990	970
16b†	295	1,516	375	122	360	655	575	440	962	338	558
16c	670	1,230	290	127	115	290	119	275	760	110	105
16d	200	760	205	350	.....	1,315	505	.....	2,305	1,510	
17†	410	1,015	455	270	380	750	460	310	400	430	430
18	760	1,150	225	170	150	250	540	339	365	410	590
19	695	1,105	352	320	265	220	305	505	860	1,080	510
20	480	1,140	250	270	310	230	1,165	154	740	410	475
21a	370	950	340	320	340	235	.....	525	.....	315	250
21b	950	1,380	425	230	960	790	950	1,450	700	1,700	730
22	1,425	1,070	450	640	910	920	980	1,140	1,560	1,100	930
23	960	630	495	220	680	620	750	.....	580	980	
24	580	695	325	335	250	310	440	270	660	360	250
25	760	1,005	250	380	870	1,275	620	1,250	965	950	
26	1,160	1,995	605	395	240	1,075	1,035	1,340	1,125	1,100	
27†	965	1,300	705	330	1,085	510	1,450	1,030	1,160		
28†	1,250	905	850	400	875	1,170	1,260	620	1,280		
Median	760	1,145	448	365	530	673	810	690	953	907	

* B. S. means "before salicyl."
† Received bicarbonate together with salicylate.

2. Diuresis is Markedly Lessened.—As indicated by the curve in Figure 2 and the data in Table 3 (from twenty-five different individuals), the excretion of urine is markedly diminished as a result of the administration of salicyl. The greatest depression is reached at, or shortly after, "toxicity," then the diuresis gradually increases and reaches practically its previous level about ninety hours after the

TABLE 4.—EXCRETION OF PHENOLSULPHONEPHTHALEIN IN THE URINES OF INDIVIDUALS RECEIVING FULL THERAPEUTIC DOSES OF SALICYLATE *

Number	Per Cent. of Phenolsulphonephthalein Excreted in Two Hours					
	B. S.	A. T.	Daily observations After "Toxicity"			End of Experiment
			1	2	3	
6	60.0	55.0	60	..	..	60.0
7	55.0	60.0	55	..	..	60.0
8	70.0	60.0	65	..	..	70.0
16b†	30.0	35.0	..	..	..	35.0
17†	50.0	50.0	..	..	..	50.0
23	50.8	26.6	53	66	75	72.0
24	68.0	74.0	60	79	98‡	88.0
25	100.0	50.0	90	100	..	100.0
26	66.0	60.0	50	62	..	68.0
27†	89.0	75.0	76	94	..	90.0
28†	70.0	48.0	62	75	..	75.2
Median§	66.0	55.0	60	77	..	70.0
13	62.0	75.0				
14	70.0	50.0				
15	74.0	25.0				
16a	25.0	35.0				
16c	35.0	45.0				
16d	35.0	45.0				
18	60.0	60.0				
19	75.0	85.0				
20	75.0	75.0				
21	75.0	70.0				
22	75.0	80.0				
Median¶	70.0	60.0				

* In this table, B. S. means "before salicyl"; A. T. means "at toxicity"; the end of the experiment was about eighty to ninety hours after administration.
† Received sodium bicarbonate together with the salicylate.
‡ Mean of 98, 88, 95, 100, 97, 88, 100, 100 and 92.5 per cent. of nine following days, respectively.
§ Used in the construction of the long curve in Figure 3.
¶ Used in the construction of the short curve in Figure 3.

administration of the drug. This diminution in water excretion is due, in part, to diaphoresis, which was usually marked, though variable, in all the subjects; and, in part, to retention; that is, edema, which we shall describe in a forthcoming contribution.

3. *Excretion of Phenolsulphonephthalein is Lessened.*—The curves in Figure 3 and the data (from nineteen different individuals and twenty-two observations) in Table 4 show that there is a diminution in

the two-hour excretion of phenolsulphonephthalein in the majority of persons after the administration of salicyl. This lasts for about twenty hours after administration is begun, and then gradually returns practically to its previous level. This diminution while relatively small, that is, about 10 per cent., is nevertheless definite, and quite constant in the majority of individuals.

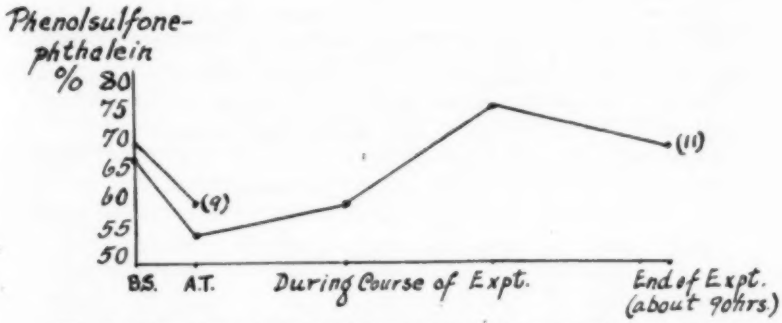

Fig. 3.—Excretion of phenolsulphonephthalein (two hours) in urine following the administration of full therapeutic doses of salicylate. B. S. means "before salicyl"; A. T. means "at toxicity," that is, about eight to ten hours after administration; daily observations were made "during the course of the experiment"; the numbers in parentheses refer to number of different individuals.

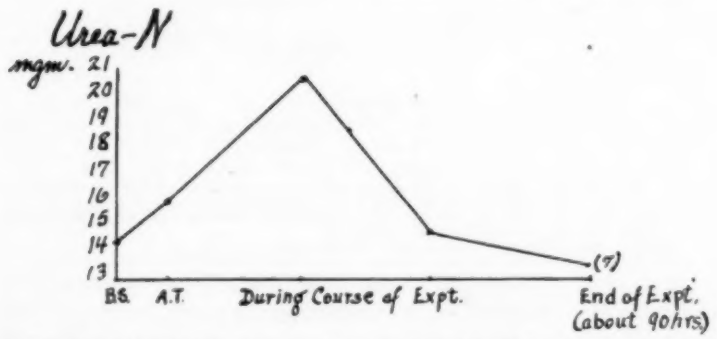

Fig. 4.—Accumulation of urea nitrogen of the blood (mg. in 100 c.c.) following the administration of full therapeutic doses of salicylate. B. S. means "before salicyl"; A. T. means "at toxicity," that is, at the end of eight to ten hours after administration; daily observations were made "during the course of the experiment"; the number in parenthesis refers to number of different individuals.

4. *Effect on the Nitrogenous Constituents of the Blood.*—Urea nitrogen: In the majority (seven) of persons in whom this was estimated, there was demonstrable a definite accumulation of urea nitrogen

in the blood. This begins to be evident about the time of "toxicity," reaches its maximum about twenty-four to thirty hours after administration, and returns to its previous level at the end of about eighty to ninety hours (three and one-third to three and three-quarter days). This is shown by the curve in Figure 4 and the data in Table 5. These seven persons represent the most complete study of the nitrogenous constituents of the blood of our series.

TABLE 5.—UREA NITROGEN CONTENT OF THE BLOOD OF INDIVIDUALS RECEIVING FULL THERAPEUTIC DOSES OF SALICYLATE *

Number	Mg. Urea Nitrogen in 100 C.c. of Blood					
	B. S.	A. T.	Daily observations After "Toxicity"			End of Experiment
			1	2	3	
22	6.4	4.3	....	....	....	6.0
23	11.5	14.3	15.6	14.0	10.0	10.1
24	9.8	12.5	20.5	14.7	12.5†	13.5
25	16.0	17.0	14.5	16.5	....	14.9
26	17.2	16.0	20.6	19.0	....	16.0
27‡	14.3	17.6	21.4	13.4	....	13.4
28‡	19.5	21.6	20.6	....	....	14.0
Median§	14.3	16.0	20.6	14.7	....	13.5
17‡	28.0	22.0				
16d	9.1	8.3				
18	9.1	6.0				
19	16.3	3.0				
20	7.4	7.6				
21	15.4	16.2				

* In this table, B. S. means "before salicyl"; A. T. means "at toxicity"; the end of the experiment was about eighty to ninety hours after administration.
† Mean of 12.3, 14.2, 12.1, 15.6, 13.5, 15.5, 12.5, and 12.5 for following eight days, respectively.
‡ Received bicarbonate together with salicylate.
§ Used for the construction of the curve in Figure 4.

In a number (six) of persons from whom it was impossible to obtain blood as frequently as was desirable, the results are not so conclusive, for the greatest accumulation of urea nitrogen would occur some time after the last specimen of blood was obtained. The blood was obtained only before the administration of the drug and at "toxicity." The results are presented in Table 5. It is seen there is a definite diminution of the urea nitrogen of the blood at "toxicity" in three (Patients 17, 18 and 19), and the content in the other patients was practically unchanged. It is quite likely that the important phase in the curve of accumulation of the urea nitrogen was missed in these experiments.

Nonprotein nitrogen: The results from nine different individuals are presented in Figure 5 and Table 6. These show a diminution in the nonprotein nitrogen content of the blood at "toxicity." This persists for a day or so, then gradually tends to return to its previous level at the end of the experiment, that is, about eighty to ninety hours after administration. The different individuals showed some variations in these changes.

As to the possible explanation of this diminution in the total nonprotein nitrogen content of the blood, it is suggested that the uric acid fraction, being affected by the salicyl, is perhaps chiefly responsible. In our series no attempt was made to estimate the uric acid content of the blood, but this has been conclusively shown by Denis[6] to be diminished in the blood after the administration of salicyl in large doses, and at the same time the excretion in the urine is increased. In addition, there are many observations by others showing definitely that salicyl

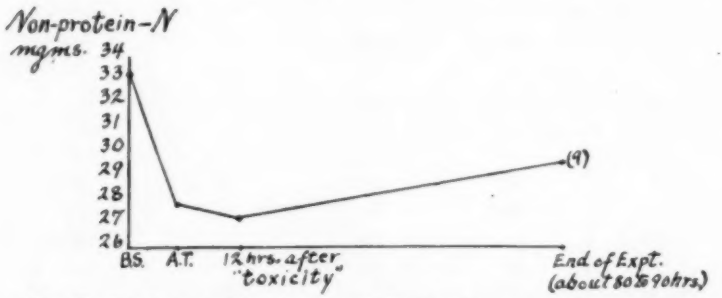

Fig. 5.—Total nonprotein nitrogen of the blood (mg. in 100 c.c.) after the administration of full therapeutic doses of salicylate. B. S. means "before salicyl"; A. T. means "at toxicity"; observations were also made twelve hours after "toxicity" and at the end of the experiment, that is, about eighty to ninety hours after administration; the number in parenthesis refers to number of different individuals.

increases the excretion of uric acid in the urine. The extent or degree of diminution in the total nonprotein nitrogen of the blood would to a certain extent depend on the content of the uric acid fraction before the administration of the drug, and in part on the functional state of the kidney. Because of this peculiar effect of the salicyl on the uric acid fraction, it appears that a study of the total nonprotein nitrogen content of the blood cannot serve as a reliable index of renal functional efficiency in individuals receiving large doses of the drug.

5. *Effect of Bicarbonate on the Albuminuria and Renal Functional Changes.*—It has been claimed (notably by Glaesgen[7] for human beings,

6. Denis: Jour. Pharm. and Exper. Therap., 1915, **7**, 255.
7. Glaesgen: München. med. Wchnschr., 1911, **58**, 1125.

and Frey[8] for rabbits) that the administration of bicarbonate together with salicylate, or rendering the urine alkaline during salicyl medication, tends to lessen or inhibit the albuminuria. Ehrmann,[9] who was not convinced that salicyl always caused albuminuria, claimed that alkalinity had no influence on the excretion of albumin in individuals in whom albuminuria occurred.

The results obtained by us do not support the claims that have been made for the beneficial effects of bicarbonate. Patients 13, 16b, 17, 27 and 28 received bicarbonate, together with salicylate, and the majority

TABLE 6.—TOTAL NONPROTEIN NITROGEN OF THE BLOOD OF INDIVIDUALS RECEIVING FULL THERAPEUTIC DOSES OF SALICYLATE *

Number	Mg. of Nonprotein Nitrogen in 100 C.c. of Blood			
	B. S.	A. T.	12 Hours After "Toxicity"	End of Experiment
5	33.1	24.0	26.9	29.4
6	42.5	49.6	54.6	76.6
7	30.6	44.6	41.6	16.6
8	27.5	35.5	27.5	10.2
9	33.3	48.2	49.2	39.3
10	24.0	14.2	16.5	19.5
11	31.1	24.1	21.3	24.3
12	40.6	29.4	14.1	
16b†	35.1	20.9	....	43.3
16c	35.1	19.7	....	30.0
Median‡	33.2	27.8	27.2	29.4
12	66.3	63.1		
13	52.2	42.3		
14	52.2	52.5		
15	53.1	63.2		

* In this table, B. S. means "before salicyl"; A. T. means "at toxicity"; end of experiment was about eighty to ninety hours after administration.
† Received bicarbonate together with salicylate.
‡ Used for the construction of the curve in Figure 5.

showed albuminuria, and of about the same degree and duration, diminution in water and phenolsulphonephthalein excretion, and accumulation of urea nitrogen in the blood. The results for these may be seen in Tables 1, 2, 3, 4 and 5. The urines of Patients 13, 16b, 17 and 27 remained alkaline throughout the experiment, and of Patient 28 only about forty hours after the administration was begun.

8. Frey: München. med. Wchnschr., 1905, **52**, 1326.
9. Ehrmann: München. med. Wchnschr., 1907, **54**, 2595.

Accordingly, bicarbonate has practically no demonstrable influence on the albuminuria and the changes in renal functional efficiency produced by the administration of salicyl in full therapeutic doses.

CONCLUSIONS

1. The administration of salicylate in full therapeutic doses invariably causes the appearance of albumin, white blood corpuscles and granular casts or cast-like bodies in the urines of normal, rheumatic, nonrheumatic, febrile and afebrile persons.

2. The albuminuria is not of febrile origin, but due directly to the drug.

3. A pre-existing albuminuria is aggravated by the administration of salicylate.

4. So far as renal functional efficiency is concerned, there is a diminution. This is indicated by, (1) lessened water excretion [taken in connection with (2) and (3)]; (2) diminished phenolsulphonephthalein excretion, and (3) accumulation of urea nitrogen of the blood.

5. The administration of bicarbonate together with salicylate has practically no demonstrable influence on the albuminuria and renal functional changes produced by the salicyl.

THE INFLUENCE OF NONSPECIFIC SUBSTANCES ON INFECTIONS *

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The therapeutic measures used in the treatment of infections may be divided into two general classes: first, those specific substances which are supposed to destroy the infecting organism or neutralize its toxins, and second, those which aim to strengthen the natural processes that normally bring about recovery.

Of the specific substances which either destroy the infecting organism or render toxic products innocuous, we have specific antiserums and certain chemotherapeutic substances. Among the most effective antiserums may be mentioned diphtheria antitoxin, tetanus antitoxin, antimeningitis serum, and a serum for the treatment of one form of pneumonia. Many others have been prepared, but there is still some doubt as to their real value as therapeutic agents. Of the chemical substances which have a direct destructive action on the infecting organisms, quinin, salvarsan and emetin are probably the most important.

Bacterial vaccines, autogenous and stock, have been extensively used in the treatment of infections with the hope that they might cause an increased production of immune substances. Curative vaccine treatment rests primarily on the assumption that under certain conditions the production of specific antibodies can be increased by the injection of the bacteria causing the infection.

Originally, it was the belief that vaccines were indicated in those conditions in which the infecting organisms are localized and more or less encapsulated and thus unable to stimulate the body to produce a sufficient number of immune bodies to bring about recovery. According to these views it will be seen that the use of vaccines as a curative measure was restricted to localized infections.

It is a debatable question whether the practical results support the hypothesis on which specific vaccine therapy is based, and it will be difficult to explain by this hypothesis the results now being obtained in the treatment of acute systemic infections. In these conditions the infecting organisms are widely distributed through the body and should

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* From the Departments of Pathology and Experimental Medicine, Vanderbilt Medical School.
* Harvey Lecture, Feb. 17, 1917.

furnish the stimulus needed to call forth an abundant supply of antibodies.

When we compare the number of infectious conditions which a physician is called on to treat with the number of specific therapeutic substances at his command, it will be seen that in the great majority of instances he is compelled to rely on the use of agents which merely serve to strengthen and to sustain his patient. Recovery in these cases depends almost entirely on the gradually increasing concentration or activation of the normal protective agencies of the body, and the final results depends on the patient's ability to resist the infection until this stage is reached.

The work done in most of the experiments made to find curative agents for the various infections has evidently been based on the assumption that a substance must be found which will act directly on the infecting organism, or that will cause a mobilization of those specific immune bodies which we are accustomed to look on as the means nature uses to bring about recovery. And yet one finds a considerable accumulation of evidence, both from the laboratory and from the clinic, which definitely indicates that certain nonspecific and as yet ill-defined factors have a large share in bringing about recovery from disease. While the emphasis placed on certain phases of immunology and specificity, more especially the fruitful antigen-antibody conception of Ehrlich, has been of inestimable value, I am inclined to believe that it has resulted in the neglect of certain perfectly obvious lines of approach to medical problems.

SPECIFIC VACCINES

That specific vaccines are effective in the treatment of acute general infections is shown by numerous reports. In 1893, Fränkel[1] treated 57 typhoid fever patients by subcutaneous and intramuscular injections of typhoid bouillon cultures sterilized at 62 C., with excellent results. Petruschky,[2] in 1902, and von Peskarola and Quadrone,[3] in 1908, obtained similar results. During the Balkan war of 1913, Petrovitch,[4] inoculated subcutaneously 460 typhoid fever patients with typhoid vaccines, with a mortality of 2.9 per cent. Of 220 patients not treated in this manner, 12.8 per cent. died. Biedl[5] states that Wiel treated 14 children suffering from typhoid fever, without a single death, and that von Variot treated 69 patients by this method with excellent results. It must not be forgotten, however, that the mortality among children affected with typhoid fever is usually low.

1. Fränkel, E.: Deutsch. med. Wchnschr., 1893, **19,** 985.
2. Petruschky, J.: Deutsch. med. Wchnschr., 1902, **28,** 212.
3. Von Peskarola, B., and Quadrone, C.: Ztschr. f. inn. Med., 1908, **29,** 989.
4. Petrovitch: Quoted by Biedl; see footnote 5.
5. Biedl, A.: Prag. med. Wchnschr., 1915, **40,** 53.

Göer[6] treated successfully 9 cases of the same disease with a soluble albuminous product obtained from typhoid bacilli, and Krumbhaar and Richardson[7] observed favorable results in 77 cases treated subcutaneously with typhoid vaccines. These authors also found in the literature records of 1,800 cases of typhoid fever in which the patients were treated with subcutaneous injections of typhoid vaccines with favorable results.

During the past two or three years the methods of using vaccines in the treatment of acute general infections have undergone revolutionary changes. Ichikawa,[8] in particular, was instrumental in bringing about this change. This author gave intravenous injections of sensitized typhoid bacilli to 87 patients with typhoid fever. Immediate recovery, so far as fever and general toxic symptoms are concerned, followed the intravenous injection of one to two doses of the vaccines. Slight hemorrhages were observed in a few instances. Biedl[8] treated 21 patients with typhoid fever by the intravenous injection of typhoid vaccines prepared by various methods. Of these 21 cases, 2 patients died as a result of uncontrollable hemorrhages from the nose. Of the 19 remaining, 17 made immediate recoveries so far as temperature and toxic symptoms were concerned, one had a recurrence with an associated bronchopneumonia and died, and one patient had a slight recurrence which subsided immediately after a second dose. In discussing the explanation of these results he states that they may be due to the action of protein split products, aided by the mobilization of immune bodies, as was suggested by Ichikawa. Gay[9] treated typhoid fever patients with intravenous injections of sensitized typhoid bacilli, and states that the course of the disease was favorably influenced in 66 per cent. of the cases.

The above references show the results of the treatment of acute general infections by injections of specific vaccines. While the results may not have been entirely uniform in character, sufficient evidence is afforded to show that the older ideas concerning the principles on which vaccine therapy were based do not afford a satisfactory explanation.

NONSPECIFIC

Matthes,[10] early in the development of tuberculin therapy, demonstrated that to all intents and purposes the reaction considered specific for tuberculin could be produced when deutero-albumose was used, and he showed that whatever difference did occur could be explained by

6. Göer, F.: München. med. Wchnschr., 1915, **62**, 1312.
7. Krumbhaar, E., and Richardson, R.: Am. Jour. Med. Sc., 1915, **149**, 406.
8. Ichikawa, S.: Ztschr. f. Immunitätsforsch., 1915, **23**, 32.
9. Gay, F. P.: THE ARCHIVES INT. MED., 1916, **17**, 301.
10. Matthes, M.: Deutsch. Arch. f. klin. Med., 1894-1895, **54**, 39.

the fact that the tuberculin fraction contained certain toxic peptones in addition. Matthes, later, went even furthe. expressing the idea that fever in general was produced by protein split products, and he suggested the importance of proteolytic ferments in this connection, thus foreshadowing the work of Vaughan in this country and the later German workers in anaphylaxis.

Fränkel,[1] in 1893, was probably the first to demonstrate the value of typhoid vaccines in the treatment of typhoid fever, and his report was followed almost immediately by that of Rumpf,[11] who obtained similar favorable results with a vaccine composed of the bacillus pyocyaneous. The medical profession, however, could see no merit in a nonspecific method of treating infections, therefore the entire subject was dropped for a considerable period. In this country, too, the controversy occasioned by the Schäfer vaccines is pertinent. Here was a biologic product, which, according to the observations of many competent observers, did at times produce striking results in a variety of infectious diseases; whether or not it was a safe remedial measure, or whether it had defects, is not pertinent in this connection. The very fact that it did certain things at times should have led to a study of why such favorable changes were brought about. The fact that it was palpably nonspecific, however, was sufficient to warrant the stamp of disapproval by the medical profession.

Within the last three years, however, this view has been gradually changing, and it is significant to note that Wright,[12] than whom, of course, no one man has stood out more emphatically for specific therapy, recently made the following statement in this connection:

> All of those who have had much experience with vaccines will have seen cases where therapeutic effects, lying quite outside the range of the particular vaccine employed, and therefore, as we thought, not quite creditable to science, have been obtained with vaccine therapy.

Schmidt[13] is among those who have observed that following vaccine therapy of any kind the body becomes resistant to a variety of commoner infections. He also called attention to the relatively low "infection index," as he termed it, which is present in carcinoma and pregnancy, and refers to Rokytansky's ideas on the antagonism between carcinoma and tuberculosis.

Von Wagner[14] utilized a similar nonspecific method when he obtained favorable results in patients with progressive paralysis treated with tuberculin. He had observed, as had others, that intercurrent infections frequently cause a remission of symptoms in this disease

11. Rumpf, T.: Deutsch. med. Wchnschr., 1893, **19,** 987.
12. Wright, A.: Brit. Med. Jour., 1915, **1,** 625.
13. Schmidt, R.: Med. Klin., 1910, **6,** 1690.
14. Von Wagner, J.: Wien. med. Wchnschr., 1909, **59,** 2124.

which sometimes last for a long period. This led him to experiment first with tuberculin alone, and later with a combined tuberculin-antiluetic treatment. He believed that he got better results with the combined treatment than with the antiluetic treatment alone. Pilcz[15] observed similar good results with tuberculin, while Donath,[16] noting the same influence of intercurrent infections in paretics, suggests the formation of abscesses in these patients by injecting turpentine into the subcutaneous tissues.

It is not intended here to recommend the use of tuberculin in the treatment of paretics, because it hardly seems warranted, but to indicate the same general phenomenon of a therapeutic effect from a non-specific method.

It is in the domain of coagulation disturbances that therapy of this nature has received particular attention in the past. The beneficial effects of subcutaneous serum injections in hemophilia is well recognized, although here too the exact mechanism is unknown. Originally, the slight leukocytosis was regarded as the potent factor, but for this there is no proof. Results have been obtained with homologous and heterologous serums, and with whole blood; but decisive results depend considerably on the dosage, and marked fluctuations in the coagulation time frequently occur following these injections. That such injections do not alter the disease process through supplying directly some deficiency, but rather through stimulating the elaboration of some substance before lacking, seems to be the conclusion reached by recent workers. This would agree with the stimulating effects observed by Esch, Busse and Weber following the injection of serum and whole blood subcutaneously in tuberculosis and in pernicious anemia.

The dermatologists have had similar results within the past three years in a variety of diseases, including some cases of psoriasis which have proved refractory to other methods of treatment. Recently Engman and McGarry[17] report favorable results in the treatment of lupus erythematosus with intravenous injections of typhoid bacilli.

The therapy of typhoid fever has so far been the chief avenue of approach to the problem. A number of vaccines have been elaborated and used subcutaneously during recent years for therapeutic purposes, and the results have been, in general, very encouraging. It was not, however, until such vaccines were used intravenously that the striking pictures of complete abortion of the disease were obtained.

Ichikawa,[8] who was among the first to use the intravenous method of administering vaccines in typhoid fever, observed that the results in

15. Pilcz, A.: Wien. med. Wchnschr., 1907, **57,** 1462.
16. Donath, J.: Wien. med. Wchnschr., 1916, **67,** 1741.
17. Engman, M., and McGarry, R.: Jour. Am. Med. Assn., 1916, **67,** 1741.

patients suffering from paratyphoid fever who had been treated with typhoid vaccines were similar in every way to those noted in typhoid fever. Kraus[18] obtained similar results in the treatment of typhoid fever with the intravenous injections of vaccines composed of colon bacilli. He also treated eight patients with puerperal sepsis with excellent results. Kraus was so impressed with this form of treatment that he suggests its use with scarlet fever, plague, septicemia, etc. In addition to vaccines prepared with cholera bacilli, typhoid bacilli and paratyphoid bacilli, Lüdke[19] also used deutero-albumose. He treated twenty-three typhoid fever patients, and of these, nineteen cases were favorably influenced. There was one death in this series. Reibmayr[20] obtained similar results with colon and cholera vaccines.

Hiss and Zinsser[21] were among the first to make use of nonspecific substances in the treatment of acute infections. They used extracts of rabbits' leukocytes in the treatment of epidemic cerebrospinal meningitis, in pneumonia, and in staphylococcus infections, and believe that the course of these diseases was favorably influenced. Floyd and Lucas[22] used the leukocytic extracts in the treatment of forty-one cases of pneumonia, and report that the mortality in their series was about half that obtained in the same institution with other forms of treatment.

Miller and Lusk[23] during the summer of 1916 treated a series of patients with typhoid fever with intravenous injections of typhoid bacilli and with secondary proteoses. In this series, 20 per cent. terminated by crisis, and 20 per cent. by rapid lysis. They also treated a series of chronic, subacute and acute cases of arthritis with these preparations with excellent results, as relief was afforded in the majority of cases. The authors do not state the number of patients treated by each method, but conclude that both gave the same results. The same authors[24] recently reported a second series consisting of eighty-five patients with arthritis treated with typhoid vaccines. Forty-five of these cases were acute, four being gonorrheal. In twenty-nine of the acute cases the patients recovered promptly after one to four injections, eight showed marked improvement, six moderate improvement, and two were unimproved. Nine of these patients had recurrences. There were twelve subacute cases, ten of which cleared up completely within three to five days, and two patients were greatly improved. There were two recurrences in this group, but the patients made complete recoveries

18. Kraus, R.: Wien. klin. Wchnschr., 1915, **38,** 29.
19. Lüdke, H.: München. med. Wchnschr., 1915, **62,** 321.
20. Reibmayr, H.: München. med. Wchnschr., 1915, **62,** 610.
21. Hiss and Zinsser, H.: Jour. Med. Research, 1908, **19,** 321.
22. Floyd, C., and Lucas, W.: Jour. Med. Research, 1909, **21,** 223.
23. Miller, J., and Lusk, F.: Jour. Am. Med. Assn., 1916, **66,** 1756.
24. Lusk, F., and Miller, J.: Jour. Am. Med. Assn., 1916, **67,** 2010.

on further treatment. Nineteen chronic patients were treated, ten of which showed definite improvement.

Culver[25] reports a series of gonorrheal complications, especially arthritis, epididymitis and acute prostatitis, in which the patients were treated with a variety of vaccines composed of gonococci, meningococci, colon bacilli, and with secondary proteoses. Twenty-eight of the thirty-one arthritic patients were either completely cured or manifested a decided improvement. The twelve patients with acute epididymitis presented complete freedom from pain after the first injection.

Ziembowski[26] has recently reported on the results obtained in the treatment of 100 patients with intramuscular injections of 5 c.c. of boiled milk. He states that excellent results were obtained by this means in the treatement of septic war wounds, in erysipelas, in tuberculous bone and joint diseases, and in three cases of actinomycosis.

Matthers, in a personal communication, states that he has used various types of vaccines and pure proteins in the treatment of typhoid fever, lobar pneumonia, scarlet fever and acute arthritis. He infers from his experiments that the therapeutic results obtained in erysipelas and lobar pneumonia do not justify the use of this plan of treatment. In the other diseases mentioned his results correspond favorably with those reported by other investigators.

Manier, Petersen and I have treated thirteen cases of arthritis, of which three were acute, three subacute and seven chronic. Of the acute cases, two were definite cases of acute rheumatic fever. One of these patients, a child of 12 years, with multiple swollen, tender joints, fever, etc., cleared up entirely within twenty-four hours after a single infection of secondary proteoses, while the other, an adult female with multiple joint involvement, elevation of temperature, etc., was entirely relieved after eight injections, except for some residual pain in one shoulder. The third acute case, with a gonorrheal joint, received four injections, with only temporary subjective relief and with but slight objective change in the joint. In the three subacute cases the patients received an average of five injections, with complete relief of all symptoms and a return of the involved joints to normal in every respect.

In the seven cases of chronic arthritis there were varying degrees of disability, from slight stiffness in the milder cases up to complete ankylosis of the majority of the joints of the body in the most severe cases. The injections given the patients varied in number from two to eighteen. The results were, complete relief in three, marked improvement in three and no noticeable change in one.

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25. Culver, H. B.: Unpublished address before Chicago Institute of Medicine, Nov. 7, 1916.

26. Ziembowski, S. V.: Med. Klin., 1916, **12**, 1174.

Four patients with gonorrheal epididymitis with acute swelling and tenderness of the epididymis, urethral discharge, etc., were treated. In every case of this series there was immediate improvement following the first injection, the epididymis becoming smaller and distinctly less tender. In each patient there was complete relief, as evidenced by the return of the epididymis to its normal size and consistency, together with the disappearance of the urethral discharge and of pus from the urine.

Two patients with erysipelas were treated. One was first seen on the second day of the disease, at which time the condition involved almost the entire face, and, in addition, the mucous membrane of the mouth and of the pharynx. The patient was markedly toxic, with a temperature ranging from 100 to 103 F., and a pulse rate of 140. He was given two doses of a secondary proteose solution on successive days, following which his temperature and pulse rate promptly settled to normal, and his local condition, both on the face and in the mouth, cleared up promptly. The second patient was also seen on the second day of the disease, and while he was not so seriously ill, the symptoms did not clear up until after four injections.

The amount of secondary proteoses given by us depends on the apparent toxicity of the patient. We usually begin with 0.25 c.c. of a 1 per cent. solution and increase the dose according to the reaction obtained. When it is remembered that Lüdke,[19] Miller and Lusk,[23] and Culver[25] gave as high as 2 c.c. of a 4 per cent. solution, it will be seen that the amounts given by us are small. Subsequent experience, however, may demonstrate that the larger doses are advisable despite the more severe reactions, and particularly in arthritic cases, where the reactions appear to be associated with little or no danger. Our purpose has been to obtain some increase in temperature with a slight chill, and this reaction we can usually obtain at the first injection with 0.25 c.c. of a 1 per cent. solution. Injections were given in most instances every day. As individuals vary in their reactions, we believe it better to begin with the smaller dose and thus establish the tolerance of each patient before pushing the treatment. In no instance were there any alarming symptoms.

It is almost impossible to determine beforehand the degree of reaction which will follow these intravenous injections. Some authors believe that it depends on the severity of the disease, while others consider the concentration of immune bodies in the circulating blood more important. From a general survey of the work done, however, it appears that there is some other factor, as yet unknown, which plays an important part in determining the severity of the reaction.

Apart from the action of the vaccines, the protein split products, and the effect of both homologous and heterologous serums, observations are recorded by Smithlen,[27] Müller and Weiss,[28] and Saxl, Bruck and Kiralihyda[29] on the effect of intramuscular injections of milk, by Mitlander[30] on salt solution, and by numerous observers on the effects of dextrose solution, colloidal metals, distilled water, etc. It seems probable that the reaction and beneficial effects observed from these substances is based on a similar mechanism in all cases.

REACTION

Immediately following an injection by this method of treatment there is usually a reaction which is sometimes severe. As a rule, there is a chill from one-half to one hour following the injection, and this may last fifteen to forty-five minutes. With the chill there is an increase in temperature of from 1 to 4 F., followed several hours later by a progressive fall. Associated with the drop in temperature there is general relaxation, profuse perspiration and a rapid subjective and objective improvement. The pulse may or may not be increased in frequency. The blood pressure in our own cases was not altered. Some authors report that many of their patients had headache, nausea, etc., and again others state that the symptoms following the injections are not sufficient to cause serious discomfort. These differences may depend on the dosage used.

Following the injection the leukocytes are decreased in number, at times as low as 2,000 per cubic millimeter. This leukopenia is followed by a gradually developing leukocytosis which usually reaches its maximum in from five to seven hours. The leukocyte count has usually returned to normal within twenty-four to thirty hours.

Immediately following the injection in acute infections, such as typhoid fever, there may be a permanent return to normal temperature — termination by crisis; the temperature and general conditions may improve more slowly — termination by lysis; or, all the symptoms may return and the disease progress as usual, uninfluenced in any manner, though usually it pursues a milder course. The temperature frequently drops to subnormal and remains so for several days in those cases which terminate by crisis.

COMPLICATIONS AND CONTRAINDICATIONS

The only serious results that have followed the use of this form of treatment occurred in typhoid fever patients, but as a large majority

27. Smithlen, F.: Wien. klin. Wchnschr., 1916, **29,** 53.
28. Müller, R., and Weiss, A.: Wien. klin. Wchnschr., 1916, **29,** 249.
29. Saxl, Bruck and Kiralihyda: München. med. Wchnschr., 1916, **63,** 511.
30. Mitlander: Budapest Letter, Jour. Am. Med. Assn., 1916, **66,** 1321.

of the cases of acute general infections treated were in patients with typhoid fever, it is important to learn more concerning the danger attached to treating this class of patients with nonspecific substances.

Hemorrhage is the most serious complication reported in typhoid fever. Ichikawa[8] who used sensitized typhoid vaccines in eighty-seven cases, observed hemorrhages in a few patients one to three days after inoculation, but the frequency with which these were observed was less than that noted among the uninoculated. R. Schmidt[13] advises against its use in patients who have already had hemorrhages, or who give histories of having been bleeders. According to this author, bronchial and pulmonary complications also contraindicate its use. Biedl[5] treated eighty-four typhoid fever patients with typhoid vaccines, and two of these died from uncontrollable hemorrhages from the nose. He also believes that previous hemorrhages contraindicate this form of treatment.

Typhoid fever appears to be the only disease in which hemorrhages have been observed following this method of treatment. Kraus[18] does not mention it as occurring in his cases of general sepsis; it was apparently not observed in any of the paratyphoid cases, and Miller and Lusk[23] do not mention its occurrence in their series of more than one hundred arthritic cases.

According to R. Schmidt,[31] protein substances injected intravenously or subcutaneously tend to decrease the coagulation time, and it is well known that certain of the lower protein cleavage products also inhibit coagulation. On the other hand, the subcutaneous and intravenous injection of homologous and heterologous serums has been a favorite procedure for some time in the treatment of hemophilia.

Ichikawa,[8] Miller and Lusk,[23] and others, advise against this method of treatment in patients with organic heart disease, and Ichikawa warns against its use in pregnancy. In the opinion of Lusk and Miller its use is also contraindicated in hypertension.

The severity of the reaction is an important factor in determining whether this form of treatment should be used in any particular instance. When we consider that the strength of the vaccines of specific and nonspecific nature which have been used in the treatment of typhoid fever varied from 100,000,000 to 4,000,000,000 bacteria to the cubic centimeter, it will be seen that the danger to the patient is not so great as the severe reactions would indicate.

And now, how are we to explain the action of these nonspecific substances? Can it be explained according to our present ideas of nature's method of bringing about recovery from infection? I believe it is doubtful if our present theories on immunity will enable us to

31. Schmidt, R.: Med. Klin., 1916, **12**, 171.

explain the action of these nonspecific substances. It might be well, however, to take up in greater detail some of the explanations which have been advanced.

SELECTIVE STIMULATION

It is now the general belief that the hematopoietic organs are the chief source of antibodies, and not the tissue cells in general. As a corollary of this idea concerning the source of antibodies, it would be reasonable to suppose that any disturbance of the hematopoietic system might alter the antibody formation.

In view of these facts, it is possible that the various agents may act as stimulants of the hematopoietic tissue, thus suddenly flooding the body with immune substances, thereby overcoming the infection. According to Wright, vaccine injections were supposed to be followed by a negative phase, at least so far as the opsonic power was concerned. Contrary to this generally accepted view, Bull[32] has recently shown that this does not hold true following the intravenous injection of a typhoid vaccine in immunized rabbits. Bull noticed that the antibodies were not diminished; on the contrary, they were rapidly increased following the injection. If this is the mechanism involved, it is important to bear in mind that the stimulus itself is not a specific factor, but that the hematopoietic system has been attuned to respond to a nonspecific stimulus with the production of a specific substance.

Various investigators have stated that the results obtained with these nonspecific substances are due to the mobilization of antibodies. Thus Müller and Weiss[28] thought this was the explanation of the results which they obtained in treating the complications of gonorrhea with gonorrheal vaccines, but serologic tests failed to confirm this view. Ichikawa[8] attributed his results to the mobilization of antibodies. Kraus[18] believed at first that the phenomenon was very similar to anaphylactic shock, but concludes that the lack of specificity contradicts this view. For the same reason he believes that the results obtained are not due to a mobilization of immune bodies. Lüdke[19] found that the agglutination value of the serum of typhoid patients treated with proteoses was not changed. Reibmayr,[20] also, found no changes in the agglutinins following the injections of typhoid vaccines.

In this respect the observations of Moreschi[33] are interesting. Moreschi noted the persistent absence of agglutinins in leukemic patients who suffered from superimposed typhoid and paratyphoid infections. The patient with typhoid fever recovered, while the one with the paratyphoid infection died. Immune bodies could not be

32. Bull, C.: Jour. Exper. Med., 1916, **23**, 419.
33. Moreschi, C.: Ztschr. f. Immunitätsforsch., 1914, **21**, 410.

demonstrated in either case. The recovery of the typhoid patient indicates that agglutinins may not be essential.

Experiments which we conducted last spring caused us to believe that the results obtained in the use of nonspecific substances in the treatment of infections, were due to the mobilization of immune bodies. Dunklin, who was working with us, found a marked increase in antibodies following the intravenous injection of proteoses in immunized animals. A similar increase in agglutinins was found in two cases of typhoid fever in which the patients had been treated with the same preparation of proteoses. We have not had the opportunity to make further tests in typhoid fever patients, but repeated experiments made during the past few months have failed to show an increase of antibodies in immunized animals following similar intravenous injections. The arthritic cases do not afford opportunities for this character of investigations, therefore we have been limited in our work to animal experiments. The observations of others, however, appear to show that the mobilization of antibodies must play a minor rôle in recovery from infection following the use of nonspecific substances.

HYPERPYREXIA

It is a common clinical experience that in some diseases, among them subacute joint diseases, neuralgia, diabetes, pernicious anemia, certain dermatoses, sarcoma, etc., distinct beneficial results follow at times on some intercurrent febrile condition. May it not be, then, that these nonspecific substances influence the course of the disease by producing a high temperature?

Rolly and Meltzer,[34] Lüdke,[35] and other investigators, have reached the conclusion that high temperature (from 40 to 42 C.), artificially produced, has a favorable influence on an established infection. Heated animals were distinctly more resistant to daily injections of small quantities of bacteria, but no difference was noted when single large doses were given. They also found that agglutinins and bacteriolytic substances are produced more abundantly in animals which are kept overheated.

In his discussion of the influence of high temperatures on infection, Lüdke[35] suggests, first, the possibility of the infecting organism being killed by the heat, and second, that a more rapid and firmer combination of the antigen and immune bodies is caused at high temperatures.

Culver[25] describes an instance in which a patient suffering from both acute gonorrheal urethritis and malaria, made a complete recovery from the urethritis following chills and fever lasting four days. He

34. Fr. Rolly and Meltzer: Deutsch. Arch. f. klin. Med., 1908, **94**, 335.
35. Lüdke, H.: Ergebn. d. inn. Med. u. Kinderh., 1909, **4**, 493.

also states that one rarely sees a gonorrheal infection coexisting with fever producing diseases like pneumonia, typhoid fever and malaria. It is well known that gonococci are particularly susceptible to high temperatures, and therefore this factor may be of importance in gonococcal infections, but it is doubtful if similar importance can be ascribed to high temperatures in infections due to such organisms as streptococci, typhoid bacilli, etc.

Inasmuch as a very sharp febrile reaction almost invariably follows the intravenous injection of specific and nonspecific substances, the importance of this phase of the subject cannot be overlooked. In one of our cases we observed a reaction temperature of 107 F. within thirty minutes after an intravenous proteose injection. This high temperature was unaccompanied by a change in the pulse rate of any moment, or other untoward symptoms.

LEUKOCYTOSIS

The importance of the leukocytic reaction has been emphasized by various authors. Gay[36] and his associates believe that recovery in typhoid fever following the intravenous injection of a modified typhoid vaccine is due to a specific leukocytosis. More recently, however, McWilliams[37] has observed that this hyperleukocytosis is apparently not specific to the degree indicated by the work of Gay and Claypole, and that even normal rabbits respond with a marked leukocytosis to the intravenous injection of typhoid vaccine. This coincides with our experience. We must keep in mind, too, the fact that in typhoid fever, particularly, the normal course of recovery is not marked by a leukocytosis; on this ground alone we might be justified in seeking the influence of some other factor or factors in the recovery which follows intravenous therapy.

On the other hand, Lüdke[19] states that there was no leukocytosis in his series of typhoid fever patients who were treated with albumoses, and Reibmayr[20] makes a similar statement for his series of patients treated with typhoid vaccines. Most of those who believe that the leukocytosis is an important factor in recovery think chiefly of phagocytosis; other possibilities, however, must be considered.

Hiss and Zinsser[21] say that immunity is probably in a large degree cellular in character, not only in the sense of phagocytosis, but also in the neutralization of toxins. They conducted a series of experiments with this idea in mind, using the leukocytes of rabbits, and came to the conclusion that "leukocytic extracts have a distinct modifying and curative action on infections." They believe that the results

36. Gay, F., and Claypole, E.: THE ARCHIVES INT. MED., 1914, **14**, 662.
37. McWilliams, H.: Jour. Immunol., 1916, **1**, 259 .

are due to the neutralization of endotoxins. Opie[38] found that leukocytes injected into the pleural cavities of dogs in which a tuberculous pleurisy had previously been produced, tended to inhibit the development of the process, as those animals which received the leukocytes lived longer than the controls. Recently, Bail[39] has advanced evidence that supports this theory. He found that a strong anticholera serum would not neutralize the endotoxin obtained from cholera bacilli, but that the toxin was destroyed if it was first incubated with a fresh emulsion of leukocytes and the antiserum then added. In these experiments the leukocytes were removed by centrifuging before the serum was added. Control experiments demonstrated that the leukocytic emulsion alone did not destroy the toxin. Heating the leukocyte emulsion thirty minutes at 58 C. destroyed its antitoxic action.

Bull and I[40] showed that leukoprotease will destroy the toxic extracts of typhoid bacilli and meningicocci, and it is not improbable that a similar explanation will apply to the results obtained by Bail.

It will be seen, then, that in considering the part leukocytosis may play in the recovery from disease, we must consider other factors in addition to phagocytosis.

MOBILIZATION OF FERMENTS

Petersen and I have already pointed out that in experimental animals intravenous injection of bacteria,[41] kaolin,[42] protein split products[43] and trypsin[44] is almost invariably followed by more or less marked mobilization of serum protease and usually of esterase.

Similar reactions occur in patients following the intravenous injection of vaccines and proteoses, but not to the same degree nor with the same regularity as in animals. In considering the possible effects of such a mobilization of ferments, both protease and esterase, we must keep in mind the fact that a variety of reactions may occur. The serum protease, as other tryptic ferments, is without effect on bacteria;[45] but if we consider the source of the intoxication which occurs in the diseased organism as primarily due to protein split products derived from the bacteria, then such a mobilization of protease may be of considerable importance in the process of detoxication, as the toxic fragments are hydrolyzed to lower and nontoxic forms. Petersen,

38. Opie, E.: Jour. Exper. Med., 1908, **10,** 419.
39. Bail, O.: Ztschr. f. Immunitätsforsch., 1916, **25,** 248.
40. Jobling, J. W., and Bull. C.: Jour. Exper. Med., 1913, **17,** 453.
41. Jobling, J. W., and Petersen, W.: Jour. Exper. Med., 1915, **22,** 590.
42. Jobling, J. W., and Petersen, W.: Jour. Exper. Med., 1915, **22,** 597.
43. Jobling, J. W., and Petersen, W.: Jour. Exper. Med., 1915, **22,** 603.
44. Jobling, J. W., and Petersen, W.: Jour. Exper. Med., 1915, **22,** 141.
45. Jobling, J. W., and Petersen, W.: Jour. Exper. Med., 1914, **16,** 321.

Eggstein and I[46] have discussed this possibility in detail in its relation to pneumonia.

As a result of this action of the proteolytic ferments the diseased organism would rid itself for the time being of the toxic substances in the circulating blood, although the disease process itself, and the infecting organisms, would possibly continue in existence, causing further injury. This would seem to be the explanation of the clinical picture obtained after intravenous therapy in those instances in which only an incomplete or transitory effect results. In the majority of these cases the patient presents a considerable improvement, both subjectively and objectively, on the day or days following the injection, despite the fact that the temperature may recur or even continue uninterruptedly. This hypothesis will not, however, explain the continued wellbeing of the patients treated in the early stages of diseases such as typhoid fever. It is difficult to understand this unless it is due to cellular resistance acquired as a result of the injections.

The influence of the mobilized ester-splitting ferments is as yet obscure. In the ultimate analysis, of course, we must turn to ferments of this nature in order to dispose of the invading organism, because it is more than probable that the actual surface of the bacterium consists largely of lipoids, or intimate lipoprotein combinations, for the destruction of which esterase-splitting ferments are probably essential.

Citron and Reicher,[47] Peritz,[48] and others, state that the serum esterase is increased in patients who suffer from infections due to lipoid rich organisms such as tubercle bacilli and lepra bacilli. They believe that a high esterase titer in these diseases indicates increased resistance on the part of the host.

ANTIFERMENTS

When discussing the increased resistance to infections said to be present in some conditions, among them carcinoma, pregnancy, and as a result of vaccine therapy, I called attention to the fact that during such states a relatively high antiferment index is a well recognized accompaniment. The question arises whether this is a mere coincidence, or whether there is some causal connection between the antiferment increase and the increased resistance to infection.

Petersen and I[49] have previously shown that the antiferment power of the serum depends on the amount of unsaturated lipoids present in a highly dispersed state in the serum. Consequently, any factor which

46. Jobling, J. W., Petersen, W., and Eggstein, A.: Jour. Exper. Med., 1915, **22**, 568.
47. Citron, J., and Reicher, K.: Berl. klin. Wchnschr., 1908, **45**, 1398.
48. Peritz, G.: Deutsch. med. Wchnschr., 1910, **36**, 483.
49. Jobling, J. W., and Petersen, W.: Jour. Exper. Med., 1914, **19**, 459.

will tend to increase these lipoids, either by increasing the supply or by decreasing the utilization, will increase the antiferment titer, while conversely, any influence decreasing these lipoids, their dispersion or their unsaturation, will tend to decrease the titer.

Wright[50] worked with saprophytic and serosaprophytic organisms, and noted that the addition of antiferment to the culture medium completely checked the growth of the serosaprophytic bacteria. He also found that even the saprophytic bacteria grew less luxuriantly when no proteolytic ferment was added. The direct influence of the antiferment cannot be as simple as Wright would assume, as Rettger, Berman and Sturges[51] showed that the ordinary pathogenic organisms do not derive their protein requirements from native or even partly hydrolyzed proteins, but solely from the lowest split products. The antiferment inhibits only the action of tryptic and not the peptolytic and ereptic ferments. Of course, when we are dealing with a definite tryptogenic organism it becomes apparent that an increase in antiferment would offer an increased factor of resistance against its growth.

The immediate effect of the vaccine and proteose injections is not an increase, but a distinct decrease, in the antiferment titer for a short period of time, followed later by a rise. The exact cause of these changes in the antiferment index remains undetermined.

PHYSICAL CHANGES IN SERUM

We have recently found that there are distinct changes in the viscosity of the serum of animals undergoing immunization, and that similar changes occur in anaphylactic shock. This alteration may be of more than theoretical interest in our interpretation of the results obtained by the intravenous injections of nonspecific substances.

Weil[52] and others have recently shown that antigen and antibody may coexist in the blood of the living animal, while Joachimoglu[53] has demonstrated that in anaphylactic shock the precipitins immediately disappear. The disappearance of precipitins, which no doubt is due to their combination with the antigen, would probably bring about conditions favorable to protease activity, as Bulger[54] and others have shown that proteolysis in serums is active following the formation of precipitates. It is well to bear in mind the possibility that the changes in viscosity following the intravenous injection of nonspecific substances may cause a combination of the antigen and antibody which is

50. Wright, A.: Brit. Med. Jour., 1915, **1**, 625.
51. Rettgers, L., Berman, N., and Sturges, W.: Jour. Bacteriol., 1916, **1**, 15.
52. Weil, R.: Jour. Immunol., 1916, **1**, 47.
53. Joachimoglu, G.: Ztschr. f. Immunitätsforsch., 1911, Orig., **8**, 453.
54. Bulger, H.: Jour. Infect. Dis., 1916, **19**, 882.

already present, and thus duplicate the conditions produced when additional antigen is introduced.

Similar changes may occur in the serum of patients with acute general infections when they are treated with nonspecific substances. Under these conditions it is not difficult to understand how areas of lowered antiferment content would be obtained in which proteolysis would occur. In such instances we may have a temporary increase in intoxication owing to the hydrolysis of the native bacterial proteins to toxic substances, and then a detoxication due to their further hydrolysis. This may be the explanation of the chill which is followed by a drop in temperature, that occurs after intravenous injections of various substances. These changes in viscosity may also help to explain the fall in antiferment strength which follows the injections.

As stated before, however, these serum changes are more or less temporary in character, and will therefore not explain the permanent recovery of patients treated in the early stages of such diseases as typhoid fever.

CONCLUSIONS

According to our present views the symptoms of an infection are the result of the struggle between the infecting bacteria and their toxins, and the protective agencies of the host. Theoretically, then, the results observed might be due either to the destruction of the infectious agent with its products, or to the fact that the cells of the host become resistant to the action of these agents. In either case, from our point of view, the disease ceases to exist. Theobald Smith,[55] in 1910, said: "The effectiveness of vaccines applied in the course of acute febrile diseases, such as typhoid and pneumonia, must be accounted for by principles of which experimental medicine has as yet no definite knowledge," and this view apparently holds true at present.

That the intravenous injection of nonspecific substances exerts a marked influence on those infections in which it has been tried is very evident. It is not believed, of course, that these newer methods will cure all cases of infections. They do, however, open up new possibilities and suggest new methods for attacking infections of unknown etiology, as also those caused by organisms for which we have no specific antiserums. That all cases are not benefited does not necessarily reflect on the value of the treatment. There are very few therapeutic measures which do not have the same objection.

55. Smith, Theobald: Boston Med. and Surg. Jour., 1910, **163**, 275.

THE EFFECT OF PITUITARY INJECTIONS ON THE BLOOD PRESSURE OF FEBRILE PATIENTS*

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Although the intravenous injection of pituitary extracts into animals is usually followed by a considerable rise of blood pressure, no comparable effects have been observed after the injection of therapeutic doses of this drug into man. Thus, van den Velden[1] says that he observed no constant and striking rise after injecting the usual doses, and Behrenroth,[2] while noting a general skin pallor after intravenous injections, was unable to establish any definite and constant change in the blood pressure.

Since plethysmographic records of the arm made in this clinic showed that pituitary injections influenced the volume and form of the febrile pulse, it seemed worth while to restudy the effect of such injections in this class of patients in order to determine whether the changes observed in the pulse volume and form were accompanied by alterations in the systolic or diastolic blood pressures.

Twenty-seven observations were made on fifteen patients. Of these, six had pulmonary tuberculosis, three infectious sore throat, one Graves' disease, three lobar pneumonia, one surgical shock, and one was convalescing from typhoid fever. From 1 to 1½ c.c. of extract of the pituitary gland (pituitrin P. D. & Co.) was injected deep into the muscle of the arm. The blood pressures were taken several times before the injection, and thereafter at intervals of about fifteen minutes for a period of one hour or more. The pulse rate, temperature and rate of respiration were also noted. Aside from an occasional slowing of the pulse rate, which never exceeded ten beats per minute, no definite change in these occurred.

Before the injection the pulse was usually of a bounding character (pointed or collapsing pulse). Following the injection it could often be felt to become smaller and more sustained. This change was usually noted in the observation made fifteen minutes after the injection, and

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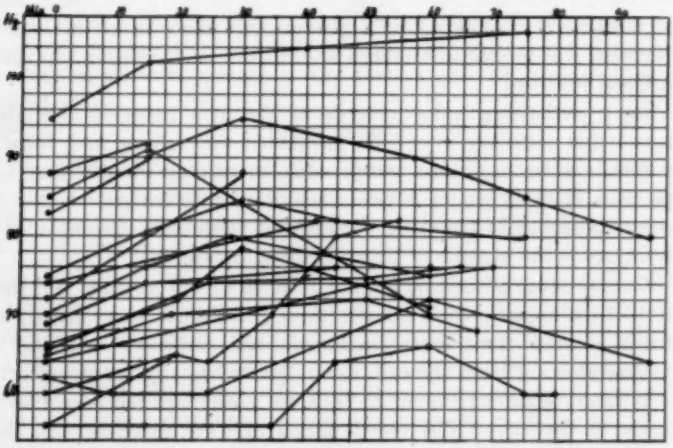
* From the Department of Internal Medicine, University of Michigan.

1. Van den Velden, R.: Die Nierenwirkung von Hypophysenextrakten beim Menschen, Berl. klin. Wchnschr., 1913, **50,** 2083.

2. Behrenroth, E.: Ueber die Einwirkung des Hirnanhangsextraktes auf den Blutdruck des Menschen nebst Bermerkungen über einige Injektions-versuche am wachsneden Tier, Deutsch. Arch. f. klin. Med., 1913-1914, **113,** 393.

it continued for an hour or more. In certain instances the change in pulse form and size was recorded by a Jaquet sphygmograph, as well as by a small volume recorder attached to a finger plethysmograph, thus demonstrating that the changes in pulse volume and form can be recorded by other methods than the arm plethysmograph.

The systolic blood pressure after pituitary injections was not altered in any constant or striking manner. At times it remained constant, at other times it rose slightly, while at still other times it fell somewhat. The diastolic blood pressure, on the other hand, which was taken by the auscultatory method, and was read at the end of the fourth phase, rose in the great majority of instances (see accompanying chart).



The effect of an injection of pituitary extract on the diastolic blood pressure of febrile patients. Note that as a rule there was a rise at the end of fifteen minutes, and that the maximum effect was observed after from thirty to forty-five minutes.

This rise was usually apparent in the observation taken fifteen minutes after the injection and reached its maximum in thirty to forty-five minutes. It therefore corresponded in time with alterations observed in the volume pulse and with the observed effects on the uterine contractions. The rise in the diastolic pressure amounted in some instances to 15 mm. Hg, or more, and this, together with its time and relative constancy, made it certain that it was due to the action of the drug. The impression was gained, furthermore, that the rise in diastolic pressure was most striking and constant when the pulse was of a definitely pointed form.

No effect on the pulse or blood pressure was observed when the pituitary extract in doses of 2 c.c., or when pituitary substance in doses of 15 gr. of the desiccated gland, was administered by mouth.

In several patients repeated injections of pituitary extract were given at intervals of two hours or more. So far as could be determined, the effects produced by subsequent injections differed in no way from the effects produced by the primary injections.

DIMINISHED BLOOD PLATELETS AND MARROW INSUFFICIENCY

A CLASSIFICATION AND DIFFERENTIAL DIAGNOSIS OF PURPURA HEMORRHAGICA, APLASTIC ANEMIA, AND ALLIED CONDITIONS *

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The two conditions, idiopathic purpura hemorrhagica and aplastic anemia, present the common symptoms, anemia and purpura. In text-book descriptions of purpura hemorrhagica and aplastic anemia there is usually no mention of a differential diagnosis between these conditions, though Naegeli[1] does briefly consider the differences, and Frank,[2] in a comprehensive paper, discusses these types of cases. Naegeli[1] and Pratt[3] confirm my own belief derived from clinical discussions, from the study of cases, reports and text-book descriptions, that these conditions are not infrequently confused with each other. Not only are these two conditions confused with each other, but also with the nonleukemic phase of leukemia, bone marrow tumors, osteosclerosis, and, at times, with pernicious anemia and types of splenic anemia, etc.

Purpura hemorrhagica is sometimes confused with the other types of purpura, and the chronic type is often undoubtedly confused with hemophilia. This confusion seems to arise from the lack of a careful study of the blood, so that from some reports (for example, those of Dean,[4] Phillips[5] and Elliott[6]) one cannot be sure of the real nature of the case reported.

The facts and thoughts expressed in this paper have been derived, not only from the literature, but also from a study of some twenty-five cases in the purpura hemorrhagica and aplastic anemia group, all of which have shown few blood platelets. Many of the cases have been studied in conjunction with Dr. Roger I. Lee, to whom I am much indebted. A few of these cases are briefly summarized at the end of the paper.

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* Submitted for publication Jan. 5, 1917.
* From the Medical Service of the Massachusetts General Hospital.

1. Naegeli: Blutkrankheiten und Blutdiagnostik, Leipzig, 1912.
2. Frank: Berl. klin. Wchnschr., 1915, **52**, 961; also 454 and 490.
3. Pratt: Osler and McCrae, Modern Medicine, 1915, **4**, 687.
4. Dean: Brit. Med. Jour., 1907, **2**, 815.
5. Phillips: Cleveland Med. Jour., 1915, **14**, 533.
6. Elliott: THE ARCHIVES INT. MED., 1909, **3**, 193.

PURPURA HEMORRHAGICA

Purpura hemorrhagica may be considered as a condition in which we have bleeding from one or more mucous membranes, often with purpuric skin lesions, associated with a diminution of blood platelets, a delayed bleeding time, and a nonretractile soft blood clot. The coagulation time is normal or slightly delayed, rarely much delayed. Purpura hemorrhagica is perhaps more usually secondary (Pratt,[5] Matthews and Carpenter[7]) to some recognized disease, as diphtheria or tuberculosis, and likewise is considered secondary when it accompanies aplastic anemia, leukemia, bone marrow tumors, pernicious or splenic anemia, etc. In such conditions it is a symptom. When it is not secondary to a recognized disease, it then constitutes what is often regarded as a disease entity called purpura hemorrhagica, the synonyms of which apparently are essential thrombopenie, pseudohemophilia, and sometimes Werlhof's disease.

Idiopathic purpura hemorrhagica is a disease that may be acute, subacute or chronic, of a continuous or intermittent nature — in some instances lasting over twenty years. A congenital and hereditary type exists.

Purpura hemorrhagica has been especially studied by the French, notably by Hayem[8] and Bensaude and Rivet[9] In this country Coe[10] first reported cases of the chronic type. Duke[11] has made careful studies on purpura hemorrhagica clinically and experimentally.

APLASTIC ANEMIA

The term acute aplastic anemia, as a disease entity, should be reserved for a disease whose etiology is unknown and which runs an acute, progressively downward, fatal course of about three to six weeks' duration, occurring especially in individuals between 15 and 30 years of age. Fever frequently occurs. There is no evidence of increased blood destruction, as in pernicious anemia. Whatever the cause of the disease may be, we are bound to suppose that its chief effect is to inhibit the formation of all new elements from the bone marrow, for at necropsy the marrow of typical cases shows practically complete fatty degeneration.

Aplastic anemia has become best recognized as a condition simulating, but to be sharply differentiated from, Addisonian anemia (pernicious anemia) and the so-called degenerated secondary anemias. The

7. Matthews and Carpenter: Am. Jour. Med. Sc., 1911, **143,** 36.
8. Hayem: Presse méd., 1895, p. 233.
9. Bensaude and Rivet: Arch. gén. de méd., 1905, **1,** 193.
10. Coe: Jour. Am. Med. Assn., 1906, **47,** 1090.
11. Duke: THE ARCHIVES INT. MED., 1912, **10,** 445; ibid., Jour. Am. Med. Assn., 1910, **55,** 1185.

papers on this condition by Musser, Jr.,[12] Cabot,[13] Lavenson,[14] Heubner[15] and Larrabee[16] are noteworthy. But as a terminal event in ordinary pernicious anemia the marrow may become exhausted or a terminal aplasia occur. In such an instance we should refer to a secondary aplasia. Aplasia of the marrow resulting from an osteosclerosis or infiltration of the marrow with leukemic or tumor cells, falls into another class and will be referred to later.

During the course of certain recognized infections, as in various types of sepsis, malignant endocarditis, typhoid fever, diphtheria, miliary tuberculosis, and more rarely in pneumonia, aplasia or exhaustion of the marrow may occur, which contributes to the fatal termination of such a case. In such instances we should speak of a secondary aplastic anemia, as we do a secondary purpura hemorrhagica, because we recognize some existing disease in the course of which aplasia or exhaustion of the marrow develops. It is perhaps best to consider that such an aplasia is due to some peculiar nature of the toxin produced by the organism causing the recognized disease in the individual case, and perhaps coupled with some congenital weakness of the marrow as suggested by Webber.[17]

The difference between the secondary and idiopathic cases of aplastic anemia may be summed up by saying that in the former we recognize a source for toxin formation and in the latter we do not. The blood picture in both may be identical and at times the character of the marrow at necropsy. In cases exhibiting sepsis, especially those with oral sepsis, we must distinguish the resulting anemia of a septic infection and the sepsis occurring from the lowered resistance of the body due to the aplasia. The latter is the type occurring in the idiopathic cases of aplastic anemia.

BLOOD PICTURE OF APLASTIC ANEMIA

In aplastic anemia the blood picture shows no evidence, or very little evidence, of regeneration of the red cells, platelets and polynuclear leukocytes; that is, of any of the three formed elements of the blood that originate in the bone marrow. The red cells appear quite well filled with hemoglobin. The color index averages 0.8,[18] often slightly higher. There is little or no variation in shape and little variation in size. Polychromatophilia, stippling, blasts, reticulation of red cells and Howell-Jolly bodies are absent or rare. Thus the red cells in an

12. Musser: THE ARCHIVES INT. MED., 1914, **14,** 275.
13. Cabot: Osler and McCrae, Modern Medicine, 1908, **4,** 637.
14. Lavenson: Am. Jour. Med. Sc., 1907, **133,** 100.
15. Heubner: Folia haemat., 1915, **19,** 347.
16. Larrabee: Am. Jour. Med. Sc., 1911, **169,** 57.
17. Webber: Proc. Roy. Soc. Med., 1914, **7,** 184.

ordinary stained smear appear not much altered from normal, which is a rather striking fact when the red count and hemoglobin are found very low, the red count often reaching 500,000 before death. In any other condition, with such low red counts as occur in the course of aplastic anemia, we find a greater change in the cells from normal. Should the color index be high, and should we find an occasional and unduly large, and especially an oval shaped, erythrocyte, but the other characteristics of aplastic anemia, we should suspect that though we had a case of aplasia of the marrow, it had developed from a case of pernicious anemia, as Musser[12] has pointed out.

The platelets in the blood in cases of aplastic anemia are markedly diminished, often nearly absent. Their character has not been reported on, though it has been noted[18] that in general when platelets are few they are usually large. In one case, which I have examined with this point in mind, they seemed to be often abnormally large; while in another case they were usually about normal size, occasionally small and some were definitely large, but not markedly so. The white count shows a leukopenia more marked as the disease progresses. This leukopenia consists in an absolute diminution of the polynuclear cells, and usually in disappearance of eosinophils, with thus a relative but not absolute lymphocytosis. The lymphocytes in my five cases like other cases (Musser,[12] Cabot[13]) varied from 45 per cent. to 92 per cent., averaging 73 per cent. They remain of the normal type. I have found no reports on the character of the polynuclears. The few polynuclears I was able to observe in three cases showed in each case normal types. It seemed, however, as if the single and double lobed types were more plentiful than normal, so that there occurred a "left-handed shift" (Arneth), which is in contrast to the frequent "right-handed shift" seen in pernicious anemia as pointed out by Briggs.[19]

THE BLOOD IN CLEAR CUT CASES OF PURPURA HEMORRHAGICA

The only constant and striking feature in the blood of cases of purpura hemorrhagica is the marked reduction of blood platelets. I have recently described in detail a typical case.[20]

The blood picture in typical cases of purpura hemorrhagica is consistent with a bone marrow which is unable to form platelets, but to a greater or less degree is able to produce polynuclear leukocytes and red cells.

The anemia in these cases is largely due to the hemorrhage and not apparently to a lack of formation or to an increased destruction

18. Kemp, Calhoun and Harris: Jour. Am. Med. Assn., 1906, **46,** 1022.
19. Briggs: Am. Jour. Med. Sc., 1914, **148,** 413.
20. Minot: Am. Jour. Med. Sc., 1916, **152,** 48.

of red cells. The red cells accordingly are of the type found in an acute or chronic posthemorrhagic anemia — variation in shape is slight, variation in size is evident—some achromia occurs, and the color index tends to be low. Polychromatophilia and stippling occur, at times a few normoblasts, and apparently rarely a Howell-Jolly body. The reticulated red cells, which seem to be an excellent indicator of the red cell activity of the marrow, are increased when definite anemia is present. The white count is somewhat elevated, usually about 12,000, rarely as high as 35,000.[3] An increased percentage of polynuclears occurs with the higher and often with the lower counts. It seems that the brisker the hemorrhage the more response there is of the polynuclear elements of the bone marrow, and likewise of the red cell elements.

In four cases of purpura hemorrhagica I have noted the type of polynuclears. Twice there was a definite "left-handed shift" (Arneth), and twice this picture was about normal, or perhaps a slight "left-handed shift" occurred.

The platelets in normal blood range from about 225,000 to 325,000 per mm.[21] In purpura hemorrhagica they are diminished, and when below about 60,000, hemorrhages tend to occur. The platelets are often markedly diminished (1,000) when the bleeding becomes severe. This is quite opposite to the marked increase, frequently to 1,000,000, seen in ordinary posthemorrhagic anemia where the blood picture is one of active bone marrow regeneration for all the three formed elements. The character of the few platelets to be seen in purpura hemorrhagica has been noted by Hess[22] to be both abnormally small and abnormally large. I have also noticed in such cases unusually small and unusually large platelets. However, they were not as large as the huge ones seen after splenectomy in pernicious anemia. The study of many bloods suggests that from the size and shape of the platelets we may obtain information on altered bone marrow activity.

BLOOD PICTURE IN CASES SUGGESTING AN INTERMEDIATE TYPE OF BONE MARROW BETWEEN APLASTIC ANEMIA AND PURPURA HEMORRHAGICA AND CONSIDERATION OF SUCH CASES — CASES CALLED PURPURA HEMORRHAGICA

Some cases of purpura hemorrhagica do not have an elevated white count. A leukopenia is occasionally present. Coe[10] pointed out that in some of his cases, as has occurred in other reported cases, as Levison's,[23] and cases I have studied, the white count was not greater

21. Wright and Kinnicutt: Jour. Am. Med. Assn., 1911, **56,** 1457.
22. Hess: THE ARCHIVES INT. MED., 1916, **17,** 203.
23. Levison: Jour. Am. Med. Assn., 1906, **47,** 936.

than 5,000 to 6,000, and not as much elevated as a similar amount of direct hemorrhage would cause in an individual whose hemopoietic system was functionating normally. Such cases suggest that the bone marrow could not respond as well to the stimulus received by the hemorrhage as it should, and suggest, further, that there may have been some depression of the white cell elements of the marrow. This, of course, suggests a transition towards an aplasia that involves the platelets markedly, the white cell elements of the marrow slightly, but not the red cell elements, for in such cases regenerative forms are frequent, though not abundant. Again, at times one may see in some cases with a normal or slightly increased white count a slightly increased percentage (50 per cent.) of the lymphocytic cells, which would likewise suggest a lack of response of the polynuclear elements of marrow. Other cases, as Case 5, presenting a chronic anemia without any signs of increased blood destruction and without much loss of blood, show red cells of a character that strongly suggest poor erythrocytic activity of the marrow. The white cells in these cases show a leukopenia with slight relative and absolute diminution of the polynuclears. The platelets are of course diminished in numbers, but only enough to cause mild purpura hemorrhagica symptoms. Such cases often spontaneously get somewhat better, only eventually to relapse. These cases suggest a midway stage between purpura hemorrhagica and aplastic anemia.

We should also note that cases approaching these intermediate cases are those of true aplastic anemia, like one I have recently seen (as evidenced by the blood picture, rapid course of the disease and yellow fatty marrow), that show during the earlier course of the disease less evidence of aplasia than others, as evidenced especially by the presence of a few reticulated cells rather than none, and the presence of a slight leukopenia and slight lymphocytosis rather than a marked leukopenia and marked lymphocytosis. In other words, one can find cases in which the blood picture can be interpreted as showing all degrees of involvement of the three elements of the marrow equally or unequally which belong to this group of cases called purpura hemorrhagica. These intermediate cases seem related to the more clear cut disease known as idiopathic purpura hemorrhagica, in that, in common, the nature of the process is unknown, the most marked symptom is purpura or bleeding, and the most striking blood finding is the diminution of blood platelets. As yet, inadequate data do not permit the assumption, but certainly suggest, that all these conditions with diminished platelets and purpura are essentially similar, even if in some cases the lesion is wholly situated in the marrow and in others is referable to increased platelet destruction in the plasma, which will be referred to later. The disease process is always directed intensely towards the

platelets, at times exclusively and specifically so. In some cases, however, this process acts less specifically and involves to a varying degree the other elements of the bone marrow in addition to the platelets.

Cases of this intermediate group are comparable to the partial aplasia produced in many instances by benzol. The action of this drug seems most marked on the polynuclear elements of the marrow, next on the platelets and the red cells. Cases of benzol poisoning had best be called by this name, as here we have a clearly recognized poison that acts on the marrow, the purpura hemorrhagica becoming a symptom of the poisoning and the aplasia of the marrow the pathology of the condition.

Cases also suggesting an intermediate type of disease between aplastic anemia and purpura hemorrhagica are those of a unique character reported by Larrabee[16] and also by Turk.[24] These are cases having the blood picture of aplastic anemia that remitted, finally to relapse and result in the death of the patient.

It is to be noted that in those conditions which we call typical aplastic anemia the red cells and white cell elements are involved before the platelets, so that there is a definte degree of anemia established before hemorrhage occurs. In the types of purpura hemorrhagica the platelets are involved at the onset, so that the hemorrhage appears early, before the anemia is especially evident. In some cases reported[25] of aplastic anemia the hemorrhage has been the first symptom. But it is not the hemorrhage that has caused the anemia here. Rather, these are cases in which the platelet elements are especially involved early and generalized aplasia immediately follows. Or we can perhaps better explain such an instance by the fact that an acute generalized aplasia will be evidenced first in the platelets, because the life of the platelets is but three to five days, and that of the red cells definitely longer, ten to fourteen days. That is, the platelets circulating in a body not forming new platelets or red cells, will disappear before the circulating red cells.

STIMULATION OF THE MARROW IN THESE CASES

One must scrutinize the cases of purpura hemorrhagica and aplastic anemia as one does other cases of "blood disease," not only from the standpoint of marrow activity, but with reference to the degree of stimulation the marrow can receive, for example, from transfusion. One should follow not any of the three formed elements originating in the marrow, but all of them in a similar fashion to that used by Lee,

24. Turk: Quoted by Frank (see footnote 2).

25. Steinhaus and Stordeur: Arch. de méd. exper. et d'anat. path., Paris, 1908, **20,** 205. Hirschfeld: Berl. klin. Wchnschr., 1906, **43,** 544.

Minot and Vincent[26] in their splenectomized cases of pernicious anemia. The study of the absolute and relative numbers of the polynuclear leukocytes, the reticulated red cells and platelets is of special importance in determining the degree of activity of these three formed elements originating in the marrow.

In aplastic anemia there is no evidence of regeneration or activity of the marrow as reflected in the blood picture, and following transfusion there will be no evidence of a stimulation of the marrow by this procedure.

The degree of involvement of the marrow in purpura hemorrhagica cases and the intermediate group of cases can be further judged by the resulting stimulation of the marrow by such a procedure as transfusion.

In some cases of purpura hemorrhagica one sees all of the bone marrow elements favorably affected after transfusion; in other cases, only the red cells and polynuclears in varying degrees. It is to be noted that a *permanent* rise of platelets is best referred to a stimulation of the marrow and not to a filling up of the patient with normal blood relatively rich in platelets. The slight *immediate* rise in the platelets in such cases, following a transfusion with the accompanying temporary cessation of the hemorrhage, is referable to a simple replacing of the lacking element, while a *permanent or a marked rise even if but temporary,* is a sign of an increased activity of the diseased marrow, provided we suppose there is not previously an abnormal rate of destruction of platelets that becomes lessened.

In some cases transfusion will add to the red and white cell elements of the marrow a stimulation beyond that which it has already received by the hemorrhage, yet the platelet elements will be but slightly affected. In other cases, especially those referred to as intermediate types of purpura hemorrhagica, the effect of transfusion on either or both the red and white cells will be slight, suggesting further that the activity of these cells in the marrow is depressed. We may conceive of a partial general aplasia in such instances.

Such cases as Case 5 may be capable of some mild stimulation, but even after transfusion, never exhibit as marked stimulation of the red and white cells as is seen following hemorrhage in some of the more sharply defined types of purpura hemorrhagica.

It is also to be noted that in some instances following transfusion one may see a temporary depression of the marrow, later followed by a stimulation or by simply a return to the state before transfusion. I have seen, for example, three instances of mild secondary purpura hemorrhagica developing in cases of pernicious anemia associated with increased diminution of platelets and increased polynuclear leukopenia

26. Lee, Minot and Vincent: Jour. Am. Med. Assn., 1916, **67,** 719.

and diminished reticulated cells, some twenty-four hours after transfusion. Also, for example, I have seen a case of idiopathic aplastic anemia, which showed before several transfusions a white count of 2,000 to 3,000, with 50 to 60 per cent. polynuclears and 0.2 to 0.7 per cent. reticulated cells, exhibit evidence of an increased depression of the marrow that was left to functionate, as evidenced by the white count becoming 1,000 to 2,000, the polynuclears 30 to 40 per cent., and the reticulated red cells entirely disappearing the day after transfusion. The bleeding in this case, however, was controlled by transfusion, presumably by the transfused platelets.

In cases of benzol poisoning, if the source of poisoning is removed, we might then expect that as the body cannot hold benzol the marrow would begin to regenerate. This occurs in the mild cases, but in the severer cases it seems the marrow is so severely injured that there is no regeneration, and death ensues. It seems, however, that if cases of the severer type are tided over a period of time by repeated transfusions, recovery can take place. Such an instance is reported by McClure,[27] the same case studied by Minot, Denny and Davis.[28] This suggests that the poison has acted to "spring some trap" that prevents a regeneration unless sufficient time is given for its release or sufficient repeated efforts at stimulation finally allow the marrow to react favorably.

This, in turn, suggests that if one obtains no result from one transfusion in idiopathic purpura hemorrhagica cases, he should, if possible, repeat the procedure. Of course in benzol poisoning, the cause being removed, one may rightly hope for the ultimate restoration of a damaged marrow. In purpura hemorrhagica, since the cause is unknown, success depends on unknown factors.

ABNORMAL DESTRUCTION OF PLATELETS AS POSSIBLE CAUSE FOR PURPURA HEMORRHAGICA. CONSIDERATION OF PATHOLOGY

The presence of very few blood platelets in the circulatory blood in many instances can be accounted for by a marked diminution in the megacaryocytes (giant cells) of the bone marrow, cells from which the platelets are formed, as conclusively shown by Wright.[29] Diminished numbers of platelets in the blood stream, however, are not always associated with diminution of megakaryocytes. In such cases we must conceive of some other process than destruction of the megakaryocytes to account for the diminished circulatory platelets. One plausible explanation is that the platelets, as fast as they are formed, are rapidly

27. McClure: Jour. Am. Med. Assn., 1916, **67**, 793.
28. Minot, Denny and Davis: THE ARCHIVES INT. MED., 1916, **17**, 101.
29. Wright: Jour. Morphol., 1910, **21**, 263.

destroyed in the circulating blood.[30] Should this occur, or should there be a destruction of the giant cells, or their ability to form platelets be altered, the cases of idiopathic purpura hemorrhagica would present, as far as we now know, quite the same blood picture.

The few reports that I have been able to locate on the pathology of the marrow in cases exhibiting before death the blood picture of pure idiopathic purpura hemorrhagica have generally simply stated the marrow was reddish. I have not found in the literature any report of a careful histologic study of the marrow in these cases. Dr. Wright has kindly located notes of an unpublished case of idiopathic purpura hemorrhagica which he studied some years ago and has recently gone over with me the fixed preparations from the necropsy. Clinically, the case closely resembled Case 1. The patient, a boy of 14, suddenly began having purpuric skin lesions, followed rapidly by repeated hemorrhages from the mucous membranes and fresh crops of purpuric spots on the skin, until death six weeks after the onset. The platelets were markedly diminished. A progressive anemia of the so-called secondary type developed, with elevated white count and essentially normal percentages of polynuclear cells. The necropsy showed a red marrow, with evidence of active regeneration of the red and white cell elements. Interestingly enough, the megakaryocytes were plentiful, perhaps slightly increased above normal numbers. From the available preparations one could not tell if there was any definitely altered histologic appearance of these cells. The other findings at necropsy were hemorrhages into many organs, an otitis media and streptococcus septicemia. The latter, from the clinical chart, would seem to be entirely secondary. The picture of the marrow in this case is quite in accord with the findings of Lee and Robertson[31] in experimental purpura hemorrhagica caused by antiplatelet serum. These authors found but slight alteration in the character of the megakaryocytes and no diminution in their number. Owing to the rapidity with which the experimental animals developed symptoms of purpura hemorrhagica, it would seem that the cause of the diminished platelets was due to their destruction in the circulating plasma. The presence of a plentiful number of megakaryocytes in the human case would also suggest that the platelets were formed in normal or even increased numbers, but that their scarcity in the peripheral blood was due to an abnormally rapid and constant destruction. Unfortunately, we have no means of determining the rate or degree of platelet destruction, as we have in the urobilin tests for red cell destruction. The congenital and chronic acquired types of purpura hemorrhagica might well be comparable to the con-

30. Foa: Arch. sc. méd., Paris, 1916, **39**, 317.
31. Lee and Robertson: Jour. Med. Research, 1916, **33**, 323.

genital and acquired types of hemolytic jaundice, in the former the platelets being involved in a similar fashion as the erythrocytes are involved in the latter.

We do not have to assume that to produce idiopathic purpura hemorrhagica there must be either a destruction of platelets in the plasma or a specific toxic action to destroy megakaryocytes or bone marrow in general. We can suppose that, though these giant cells are plentiful in numbers, they become affected so that they are unable to allow platelets to be cut off from them in normal fashion. It seems that no matter which of these three pathologic processes may occur, however, and perhaps all three occur singly or together in different cases, the blood picture would be the same as far as any methods now known can tell us.

It may well be that the action of an abnormally rapid destruction of platelets in the blood stream in certain instances acts to cause, to a greater or less degree, a depression of the whole marrow.

FURTHER CONSIDERATION OF PATHOLOGY IN THIS GROUP OF CASES

Diminution of the megakaryocytes is undoubtedly the cause of the reduction of platelets in the circulatory blood in aplastic anemia, as diminution of the red and white cell elements of marrow is the cause for the diminished red and polynuclear count. In the typical cases one finds a yellow, fatty or gelatinous gray marrow with either very few normal cell elements present or none at all. There are numerous very interesting cases reported in the literature (Larrabee,[16] Frank[2]), giving apparently the blood picture of aplastic anemia, but without clear cut pathologic marrow. Such cases are a study in themselves and will be briefly referred to. Some of these cases have had but few normal cells in the marrow and have shown lymphoid-like cells. Others have shown mixtures of lymphoid areas in a fatty degenerated marrow. Still others have shown foci of normal, perhaps hyperplastic marrow in some parts, with degeneration in other parts. Such cases present a picture of an incomplete aplasia. In fact, we must remember that many cases eventually terminating with complete aplasia, during the course of the anemia do show often a few young regenerative cells, which are probably formed from the small active foci of marrow attempting to compensate the marked destructive process.

In the symptomatic cases of purpura hemorrhagica associated with leukemia or tumor infiltrations of the marrow, the megakaryocytes have been displaced by the abnormal cells so that they are very few in number, as we might expect from the few platelets in the peripheral blood.

It seems most reasonable to assume that the aplasia of aplastic anemia is caused by some unknown toxin or altered physiologic activity, acting on the whole bone marrow, the red cells being first attacked, the platelets being relatively *later* involved as evidenced by the hemorrhages occurring after the anemia has been present for some time. But in purpura hemorrhagica the platelets seem to be first affected by a specific toxin, so that the hemorrhages begin to occur before the anemia, which is, in many instances, chiefly referable to loss of blood. In other instances, the unknown toxin may eventually act directly or indirectly to cause partial or complete aplasia or exhaustion of the marrow. In those cases of purpura hemorrhagica which have been considered intermediate between purpura hemorrhagica and aplastic anemia, we may conceive of the "toxin" of such a nature that besides involving the activity of the megakaryocytes, it has also, to a certain extent, impaired the activity of either or both the red and white cell elements of the marrow.

One need not conceive of a toxin at work to destroy the marrow in such symptomatic cases of purpura hemorrhagica as those due to leukemia, marrow tumors or pernicious anemia, for here there is, as shown by necropsy studies, a displacement of normal cells by abnormal ones.

In many of the cases of chronic disease where depression or inactivity of the marrow exists, probably no toxin is at work. In such instances we could account for the inability of the marrow to form blood elements by supposing a congenital peculiarity of the hemopoietic system. Such cases as Predtechensky[32] refers to would be examples, and perhaps my Cases 6 and 7. In other instances we may conceive that the marrow of the individual has a low ability to withstand an attack by a toxin that ordinarily induces no such effect. We might perhaps conceive of the marrow depression in some instances resulting from disease of some other organ of the body, similarly as we see in disease of some of the glands of internal secretion, hyperactivity of one depressing the activity of the other. There are certain cases grouped under the title of splenic anemia without evidence of increased blood destruction in which a leukopenia with relative lymphocytosis and diminished platelets occur, and in which a purpura hemorrhagica develops. Removal of the spleen in such instances seems to inaugurate in some manner a stimulation of the bone marrow. One might, as Rendu and Widal[33] and others have suggested, consider that some overactivity of the spleen caused a depression of the marrow.

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32. Predtechensky, V. E.: Russky Vrach, 1916, **15,** 313; abstr., Jour. Am. Med. Assn., 1916, **67,** 244.

33. Rendu and Widal: Bull. méd. Soc. d'hôp., 1899, **3,** 528.

Is it not possible that at times, with or without hypertrophy of the spleen, its physiologic activity is altered so as to cause bone marrow depression? It is, however, to be noticed that in the conditions called idiopathic purpura hemorrhagica and aplastic anemia the spleen is very rarely palpable and never much enlarged. There is a group of cases described by Kleinschmidt,[34] and also by Babonniex and Tixier,[35] in children, in which there is marked evidence of blood destruction, enlargement of the spleen and aplasia of the marrow at necropsy. Such odd types of blood disease serve to show how we can find almost any combination of factors involving blood destruction and formation, and how we can find examples intermediate between the different more clear cut types of blood disease.

Let it be noted here that the various hypotheses and assumptions given above, as well as those that follow, are simply speculations and theories, and not proved facts.

FRAGILITY OF RED CELLS IN APLASTIC ANEMIA AND PURPURA HEMORRHAGICA

The fragility of the red cells to various strengths of sodium chlorid solution in a case of aplastic anemia has been studied by Musser.[12] He found that the cells began to break up in almost the same strength salt solution as they normally do, 0.47 per cent., but that complete hemolysis occurred in a greater percentage of salt solution than normal — 0.40 to 0.37 per cent., instead of 0.34 to 0.30 per cent. In one case we obtained exactly the same figures; in another it began in 0.42 per cent., and was complete in 0.36 per cent. solution. Musser considers the alteration in the maximal resistance to be due to the absence of the young red cells. Pepper and Peet,[36] however, were unable to find any abnormal fragility of the reticulated red cells, cells considered to be young red cells.

In experimental purpura caused by antiplatelet serum, Musser and Krumbhaar[37] have recently observed a decreased resistance of the red cells.

Frank[38] studied the fragility of the reds in one case of purpura hemorrhagica and found hemolysis to begin in 0.46 per cent., and complete hemolysis to occur in 0.28 per cent. solution. I found in a case with considerable anemia that hemolysis began in 0.45 per cent., and complete hemolysis occurred in 0.24 per cent. solution. The same figures were also obtained in a second similar case, while in two others

34. Kleinschmidt: Jahrb. f. Kinderh., 1915, **81,** 1.
35. Babonniex and Tixier: Arch. d. mal. du coeur, 1914, **7,** 281.
36. Pepper and Peet: THE ARCHIVES INT. MED., 1913, **12,** 81.
37. Musser and Krumbhaar: Jour. Am. Med. Assn., 1916, **67,** 1894.
38. Frank: Berl. klin. Wchnschr., 1915, **52,** 454 and 490.

with but little anemia, hemolysis began in 0.44 per cent., and was complete in 0.30 per cent. solution. Lenoble[39] refers to a case with decreased fragility, that is, increased resistance. In idiopathic purpura hemorrhagica, when anemia exists, it seems that the fragility of the red cells to varying strengths of salt solution is of the type seen with acute secondary anemia; that is, with an increased maximal resistance, while in idiopathic aplastic anemia the maximal resistance seems decreased.

CLASSIFICATION OF TYPES OF PURPURA HEMORRHAGICA AND APLASTIC ANEMIA

It is possible to conceive that aplastic anemia and purpura hemorrhagica are not so very distantly related, as also suggested by Frank.[2] We see *pure* types of purpura hemorrhagica and of aplastic anemia; also all intermediate grades. When we recognize a source for a toxin in any type, we call it secondary, while if the toxin or cause is not recognized, we call it primary, the blood picture being the same in either instance.

It seems that we can divide, and perhaps in the future shall further subdivide, into several groups these conditions involving an unknown agent that certainly acts on the marrow in some instances, and may perhaps at times act in some manner specifically on the megakaryocytes or only to destroy formed platelets in the circulating blood. These groups would appear gradually to merge from one into another. It would seem desirable at least to consider cases of purpura hemorrhagica and aplastic anemia in the same general group and not to discuss aplastic anemia under "anemias" and purpura hemorrhagica, only with the arthritic and other purpuras.

It seems to me that we can distinguish the following groups of cases, all of which have the platelets involved in some manner, and all of which occur especially in children and young adults.

1. Pure aplastic anemia Duration, weeks; always fatal.	Aplasia of all elements of the marrow; red cells especially involved.
2. Purpura hemorrhagica	Involvement of platelets only due either to interference with their formation, to abnormally rapid destruction or a combination of factors; hyperplastic or normal appearing marrow occurs in some instances.
A. Continuous: Acute or chronic; duration few days to months or even years.	
B. Intermittent or relapsing: Duration of attack days or weeks. Number of attacks two or more, over period of months or years.	

Either *A* or *B* type may terminate with aplasia or exhaustion of the marrow involving all its elements, or at any time appear as intermediate types. In

39. Lenoble: Arch. d. mal du coeur, 1913, **6**, 313.

Type 2 *A* it is to be noted that platelets are always diminished below normal. With attacks of bleeding they become more diminished, or may throughout the course of the disease remain so low that purpuric symptoms are constantly present. In Type 2 *B* the platelets are diminished below normal only with the attacks.

3. Intermediate type of bone marrow involvement usually called purpura hemorrhagica		
	This may be the end-result of Type 2, or appear as the subacute or chronic form. Duration, weeks, or more; usually over months or years; may be intermittent in the intensity of the involvement of the marrow elements.	Platelet elements of marrow involved with varying degrees of depression or aplasia of either or both the white and red cell elements of the marrow. Perhaps some platelet destruction also occurs.

Purpura hemorrhagica is hardly a satisfactory name for the disease conditions referred to — the term does well for the name of the symptoms. Aplastic anemia is a satisfactory term, but it is a term to be used only in one special group of these related cases. It would seem better if we chose more specific terms, as chronic insufficiency of the blood platelets, or, congenital hypoplasia of the marrow. Best of all, I think, is *insufficiency of the marrow with especial involvement of the platelets or other formed elements in varying degrees.* Also we should very probably refer to some cases as associated with abnormally rapid platelet destruction.

DIFFERENTIAL DIAGNOSIS OF PURPURA HEMORRHAGICA AND APLASTIC ANEMIA

We may recall here that certain poisons, as benzol, act to produce varying degrees of aplasia of the marrow, and we should not forget the possibility of such poisoning when cases of an aplastic or hemorrhagic type present themselves. Such instances as those in which we recognize the etiology should be called by the name of the poison producing the diseased condition. Purpura hemorrhagica and aplastic anemia may appear as idiopathic diseases or as conditions secondary to some recognized disease. Let us briefly consider the diseases with which purpura hemorrhagica and aplastic anemia are more usually confused.

1. Other Types of Purpura.—Purpura hemorrhagica is not to be confounded with certain other types of purpura, drug purpuras, purpura simplex, some cases of so-called Henoch's purpura, and purpura rheumatica (Schoenlein's purpura). These conditions differ in various ways from purpura hemorrhagica, but especially in that *their blood platelets occur in essentially normal numbers,* and sometimes above normal. It may also be noted that joint symptoms in purpura hemorrhagica are very rare. It seems to me that improper use of the term

purpura hemorrhagica is not infrequent; for example, Bauch[40] (1916) entitles an article, "Three Cases of Purpura Hemorrhagica in Chronic Tuberculosis." None of these cases had diminished blood platelets; they resemble more cases of arthritic purpura. These cases are not like the cases of purpura hemorrhagica in tuberculosis described by Bensaude and Rivet[41] in 1906.

2. Hemophilia.—In hemophilia the blood platelets are in normal numbers or slightly increased, though they are physiologically and qualitatively defective, as pointed out by Fonio,[42] and Minot and Lee.[43] The differential diagnosis between hemophilia and purpura hemorrhagica has been recently discussed by Hess[22] and Minot and Lee.[43] In hemophilia the coagulation time and prothrombin time of the blood is nearly always much delayed; in purpura hemorrhagica these times are rarely more than slightly delayed, and are often normal. The blood clot in hemophilia retracts in normal fashion, while in purpura hemorrhagica it does not. The bleeding time in hemophilia is essentially normal, in contrast to the delay, often marked delay, seen in purpura hemorrhagica. It is to be noted, however, that the chronic types—especially the congenital types of purpura hemorrhagica—are usually incorrectly diagnosed as hemophilia. When one hears of a diagnosis of hemophilia in females, probably the correct diagnosis is purpura hemorrhagica, as true hemophilia occurs only in males. Females of hemophilic families may, however, present this chronic type of purpura hemorrhagica. It seems that the chronic type of purpura hemorrhagica is probably more common than is usually recognized; and also that the conditions involving varying degrees of bone marrow insufficiency are probably more common than one would be led to believe from textbooks and the literature. It is quite frequent to have one's attention first attracted to these conditions by removal of teeth or minor operations on the nose and throat. With unexplained hemorrhage one should always ascertain the number of platelets and the ability of the clot to retract.

3. Nonleukemic Phase of Leukemia.—Purpura hemorrhagica and aplastic anemia are undoubtedly frequently confused with the nonleukemic phase of leukemia, when such a case presents anemia and purpura hemorrhagica as symptoms. The resemblance and the differential diagnosis between these two conditions do not seem to be commented on in most textbooks, though Hastings,[44] Lavenson,[14] and

40. Bauch: THE ARCHIVES INT. MED., 1916, **17,** 444.
41. Bensaude and Rivet: Presse méd., 1906, **14,** 469.
42. Fonio: Cor.-Bl. f. schweiz. Aertze, 1915, **45,** 1505.
43. Minot and Lee: THE ARCHIVES INT. MED., 1916, **18,** 474.
44. Hastings: Am. Jour. Med. Sc., 1905, **129,** 787.

Naegeli,[1] among others, have pointed out that cases are reported as Werlhof's disease (purpura hemorrhagica) which are probably nothing more than cases of acute lymphoid leukemia. In such leukemic cases the diminution of the platelets and red cells and white cell elements of the marrow is not due to a fatty condition of the marrow, but rather to a crowding out of the normal cells of the marrow by the tumor-like cells (myelophthisis). Usually such cases show at necropsy a red, or partly red, marrow with infiltration by the tumor-like cells. That part of the normal marrow that is left seems still capable of regenerating the red cells, white cells and platelets after normal fashion, though the amount of these elements regenerated is less than normal. Hence, anemia results, purpura hemorrhagica results, and a diminished absolute polynuclear count results. Thus, in the peripheral blood we see a picture of active compensating function of the remaining erythroblastic marrow, that is, polychromatophilic cells, reticulated cells, blasts, and cells of abnormal shape and size. Part of the picture may be due to an irritation of the marrow by the abnormal or foreign cells.

This red cell picture is in contrast to that seen in aplastic anemia and is more like that seen in purpura hemorrhagica. However, some cases exhibiting the picture seen in aplastic anemia, show at necropsy a marrow with few or no normal cells, but with a hyperplasia of lymphoid cells or a lymphoid marrow. Some of these cases remain puzzles, others perhaps are the end-results of a leukemia. Such cases would be perhaps impossible to tell from an aplastic anemia with the usual fatty or degenerate marrow unless one found numerous abnormal types of white cells in the blood smear.

In considering the differential diagnosis of purpura hemorrhagica and the nonleukemic phase of leukemia we should pay especial attention to the presence or absence of the swelling of the lymph nodes. If enlarged, they certainly suggest a leukemic nature of the disease. But unfortunately they are often not appreciably enlarged in the nonleukemic phase of leukemia, so that mistakes in diagnosis are easy.

Naegeli[1] has pointed out that sometimes in the acute cases the lymphocytosis is not very marked, so that the diagnosis must often depend on the demonstration of qualitative variations of the lymphocytes, especially the presence of large lymphocytes with pale nuclei, and on the demonstration of forms with lobulated nuclei described by Rieder and other abnormal types of cells of the lymphocyte series. The finding of a considerable number of abnormal lymphocytes is certainly of great importance in the diagnosis. In most cases, however, it seems that the lymphocytosis is apt to reach a much higher percentage (95 per cent.) than it usually does in aplastic anemia, in which the lymphocytes are normal small lymphocytes. If there is a very

high percentage of lymphocytes in aplastic anemia the red cells are markedly aplastic in character, while with a similar percentage of lymphocytes in a leukemic condition, with a low white count, the reds almost always show some evidence of regeneration. Those cases showing blood of aplastic character with lymphoid marrow are probably very rare. Some of these may be cases of "lymphoid" leukemia of myelogenous origin in the nonleukemic phase.

4. Bone Marrow Tumors, Osteosclerosis.—Bone marrow tumor, primary or metastatic, may be the proper diagnosis in a case when anemia and purpura hemorrhagica are the presenting symptoms. The clinical history, physical examination, Roentgen-ray findings and the occurrence of Bence-Jones protein in the urine in myeloma are of great help in distinguishing such cases from idiopathic purpura hemorrhagica. The blood picture may be quite similar, but the presence of abnormal cells, plasma cells, tumor cells, should they occur in the peripheral blood, may suggest the diagnosis. In such cases the liver and spleen may revert to their embryonic state so that hematopoiesis occurs in these organs. I am inclined to believe, especially from Dr. Wright's necropsy studies, that this does not occur in those idiopathic conditions we call aplastic anemia and purpura hemorrhagica.

5. Pernicious Anemia.—The diagnosis of pernicious anemia from aplastic anemia is usually simple. If, however, a case of pernicious anemia is first seen towards the ends of the disease when the bone marrow is exhausted, the blood may present a picture resembling that of idiopathic aplastic anemia. The history of remissions, of sore tongue, of symptoms of spinal cord involvement, of a skin colored to suggest increased red cell destruction, would all strongly suggest pernicious anemia and not idiopathic aplastic anemia. The blood picture in those cases of pernicious anemia that become of an aplastic nature will show leukopenia, lymphocytosis and few platelets, but one should note that the color index tends to remain high, and very abnormal shaped and large cells, though perhaps few, are found, rather than the much more normal looking cells seen in true, idiopathic, aplastic anemia.

6. Splenic Anemia.—As has been pointed out before, some cases of splenic anemia presenting few blood platelets with their anemia and no, or slight, evidence of increased red cell destruction, may be perhaps quite closely related to types of purpura hemorrhagica. In fact, if it was not for definite, often marked, enlargement of the spleen, and, later in the disease, enlargement of the liver, some cases would be indistinguishable from types of purpura hemorrhagica. Our Case 5, called an intermediate type of purpura hemorrhagica, shows a slightly enlarged spleen, and such a case may well represent a type intermediate between those cases called purpura hemorrhagica and those called

splenic anemia, in which the enlargement of the spleen is greater and precedes the anemia, which in turn becomes quite evident as a rule before the purpuric symptoms appear in these cases.

REPORT OF CASES

The following selected, briefly summarized cases serve to show examples of some of the conditions referred to in the text. Case reports of the five cases of typical aplastic anemia studied are not given, as such cases are discussed in the text and the reported cases are entirely similar. These five cases occurred in girls between the ages of 9 and 19. Three cases came to necropsy and showed the typical fatty and often serous degeneration of the marrow, with either very few or no marrow cells left. Some showed a blood picture of very severe aplasia. Others, though typical aplastic anemia, showed a few young red cells and the lymphocytosis was not high (45 to 60 per cent.), indicating that a little regenerative power of the marrow was left.

In the cases given below the complete findings are not given, but only the essential and important ones. Blood cultures and Wassermann reactions were negative in all.

CASE 1.—(W. M. 207893). *An acute idiopathic purpura hemorrhagica with fatal course. It is entirely similar to the one referred to in the text in which necropsy showed a normal or slightly hyperplastic marrow.*

A girl, aged 15, entered the hospital April 19. The history is negative except for the following: Seven weeks before entrance a tooth was pulled. After this there was oozing of blood from the tooth socket for two weeks. Four weeks before entrance her nose began to bleed and bleeding from the gums recurred. During the previous two weeks there had been excessive vaginal flow, and for about the same length of time purpuric eruption on the body. She had grown steadily paler and weaker. The patient died, April 27. While in the hospital blood oozed from all mucous membranes of the body. Only slight temporary improvement followed transfusion of 400 and 600 c.c. of blood. It is noteworthy, however, that as in the previously reported case,[20] the purpuric skin lesions decreased markedly after transfusion and no new lesions appeared, though there was only temporary influence on the hemorrhage from the mucosae. *Physical examination* revealed nothing additional of interest. The temperature fluctuated 98 to 101 or 100 to 103 F. each day.

Blood: The platelets were always very rare, or rare and of a small or normal type. There was no evidence of stimulation of these elements after transfusion. The coagulation time was normal, the clot nonretractile and soft. The bleeding time was much prolonged (often over one hour), though temporarily shortened after transfusion (three to eight minutes). The white count averaged 8,000, the polynuclears 78 per cent., lymphocytes 21 per cent., eosinophils 1 per cent. Arneth count showed a "left-handed shift."

The red count was 1,300,000 to 1,600,000. Hemoglobin 25 to 40 per cent. The red cells showed achromia, considerable variation in size and some variation in shape. Occasionally a blast was seen. Polychromatophilia and stippling were much in evidence. The reticulated cells, chiefly of a knotted type, varied from 14 to 3 per cent. The urobilin excretion was normal.

CASE 2.—(E. M. 184907). *A case of idiopathic intermittent purpura hemorrhagica. Death in the second attack. No signs of depression in the red or white elements of the marrow.*

Man, aged 33; entered hospital September 12. Four years prior to entrance the patient had an attack, lasting about three weeks, of bleeding from the mucous membranes, with purpuric spots on the skin. Eight years previous to entrance he had abdominal pain, diagnosed as plumbism. Nine days before entrance bleeding began from the nostrils, three days before from the gums, and in the previous two days there had been blood in the urine. For a week there were purpuric spots on the skin.

The patient, growing progressively more anemic, died October 14. Recurring crops of purpuric spots occurred on the body, with fluctuations in the intensity of the bleeding from all mucous membranes. The patient was not transfused. *Physical examination* never revealed any abnormalities except anemia and hemorrhages and a functional systolic murmur. The temperature during the first week was 103 to 105 and in later weeks 98 to 100 F.

The blood examination revealed practically the same findings as in Case 1, except that the coagulation time was eighteen minutes. (Normal being five to ten minutes.)

CASE 3.—(W. M. 197121). *Secondary (?) acute purpura hemorrhagica with recovery. Especially interesting because of the fact that ivy poison may well have been the toxin responsible for the diminution of platelets.*

A woman, aged 25, entered the hospital August 15, with evident severe dematitis venenata of five days' duration, due to poison ivy. August 13 a few purpuric spots appeared on the body and increased in number until August 16, when they rapidly left and were essentially gone by August 19. August 14 and 15 there was slight oozing from the gums and nostrils and blood was found in the stools and urine on the 15th. The physical examination was negative except for the findings noted above. Temperature 99 to 100 F. The patient remained well during the two years following the purpuric attack just described.

Blood: The red count, hemoglobin and red cells were normal. The white count, 12,000, and polynuclears 72 per cent.; the other white cells were chiefly normal, lymphocytes. The platelets numbered 40,000 August 15, and 176,000 August 18. The coagulation time, August 15, was very slightly delayed, but the clot was nonretractile and exhibited the reclotting phenomena.

CASE 4.—(Private Case). *Idiopathic intermittent purpura hemorrhagica. Depression of the white cell elements of the marrow and probably of the red cell elements in the sixth attack. No evidence of white or red cell depression in previous attacks.*

Man, aged 28; the man had good health until five years prior to being seen, when five days after removal of his tonsils he bled profusely from his mouth and nose for three days. In the course of seven years he had six attacks of severe bleeding from his gums and nose lasting three to twelve days. Once a few red cells were found in his urine and a few purpuric spots appeared on his body. The patient was seen in the fourth and sixth attacks. Following each attack a considerable pallor developed. His color became normal about four weeks after each attack except after the last one. Following the fourth attack the red cells rose from 2,700,000 to 4,800,000 in three weeks, but following the last attack the reds rose only from 2,800,000 to 3,700,000 in eight weeks. The patient himself noted that he did not regain his color as easily as after his previous attacks. Unfortunately, he has been lost track of. In both attacks the platelets were very scarce, increasing as the bleeding ceased. They were normal in numbers when twice observed between attacks. In the fourth attack the white count was 14,000 and the polynuclears 78 per cent., in contrast to counts close to 5,000 and polynuclears 50 per cent., with practically all the other white cells small lymphocytes in the sixth attack. The red cells in the fourth showed 13 per cent. of reticulated cells and the other evidences of a very active regeneration of red cells, in

contrast to the red cells seen in the last attack. In this last attack the red cells gave some evidence of regeneration as shown by 3 per cent. of reticulated cells, a few polychromatophilic and stippled cells, and variation in size of cells, but none of the signs of active regeneration were as marked as in the previous attack, which is likewise evident from the history given above of a much slower disappearance of his pallor.

CASE 5.—(E. M. 208209.) *A case of intermittent intermediate type of purpura hemorrhagica. Blood picture suggests some aplasia or exhaustion of not only the platelet elements of the marrow, but also the white cell elements and red cell elements. The anemia presented is not wholly explained by hemorrhage. The lack of evidence of increased blood destruction, history of the patient, and the blood picture suggest that this is not a case of pernicious anemia. What part the enlarged spleen plays in the case, the patient being a Greek, is problematical.*

A Greek boy, aged 19. Seven years prior to admission the patient had painless hematuria for two days; none since. The gums bled at that time and he thinks he may have had some "red spots" on his body. At that time he was in bed for six months on "account of weakness."

The history of his present illness showed that fourteen, eleven and five weeks prior to entrance he had a profuse nosebleed and lost at least a cupful of blood each time. For the previous five weeks he felt weak and dizzy. There was no history of sore mouth, paresthesia, gastro-intestinal symptoms or malaria.

On entrance, May 5, the physical examination showed pallor, a few small purpuric spots on the legs and a palpable spleen (dulness 10½ by 16 cm.). Otherwise the examination was entirely negative. The patient remained in the hospital until May 23, during which time he occasionally had slight epistaxis and slight bleeding from his gums, until he was transfused with 850 c.c. of blood, May 17, after which he had no more bleeding before he left, May 23. Temperature 99 to 98 F. I have unfortunately not been able to obtain any trace of this patient since he left the hospital.

Blood: The platelets were always diminished; 35,000 on one occasion, before transfusion, and 120,000 on discharge. The bleeding time on entrance was as much as one hour, usually four to eight minutes. The white count varied from 3,600 to 2,100. The polymorphonuclear neutrophils remained close to 54 per cent., the remaining cells were lymphocytic of normal type, except for an occasional transitional cell. Following transfusion the polymorphonuclears reached 66 to 60 per cent., but without any appreciable rise in the white count. The red cells remained about 1,850,000 and the hemoglobin 45 per cent. The red cells showed moderate variation in size, some variation in shape, some macrocytes, but not of an extreme type and not large oval cells. The larger cells were well filled with hemoglobin; the others showed some achromia. Very rarely a stippled or polychromatophilic cell occurred. Only one normoblast was seen in nine different examinations. The reticulated red cells were never over 2 per cent., except five days after transfusion, when they were 3 per cent. They were rarely of a knotted type and usually the reticulum consisted of but scattered strands.

CASE 6.—(W. M. 198899.) *Congenital continual purpura hemorrhagica. Not hemophilia. The circulatory blood platelets were always diminished. Bleeding from wounds occurs readily. With a downward fluctuation of the platelets they become so few that spontaneous hemorrhage occurs.*

The patient was a boy, now aged 12 years, who had been studied many times. Since he was an infant he had had innumerable attacks of bleeding from the nose, throat, gums, rarely gastro-intestinal tract, and purpuric eruptions on his skin. In the previous two years he had had three mild attacks of bleeding. Whenever he was bruised or cut from even slight injuries he bled very readily and in abnormal amounts. There had never been any joint symptoms. Neither his brothers nor sisters are "bleeders," nor is there any history of "bleeders"

in his mother's or father's family. He had measles at the age of 6, with severe hemorrhagic symptoms.

The physical examination had never revealed anything noteworthy beyond the purpura.

Blood: During five attacks, between 1910 and 1916, the platelets were 13,000 to 50,000. Between attacks the platelets have always been definitely diminished (100,000 to 200,000) though not as low as during attacks. The bleeding time has been delayed with the attacks and often slightly delayed (four to seven minutes) between attacks. The coagulation time has usually been normal, occasionally slightly delayed. The white count has been 25,000 to 8,000, higher after hemorrhages. Two observations between attacks showed 8,000 to 14,000. The polynuclear have varied from 78 to 53 per cent. The other white cells have been chiefly small lymphocytes with no abnormal types of white cells. The red count has varied from 2,500,000 following severe hemorrhage to 4,800,000 some months after the last attack. The red cells have appeared normal, or when anemia was present they have been of the type seen with posthemorrhagic anemia.

CASE 7.—(W. M. 165399.) *Another case of the continual chronic type of purpura hemorrhagica either congenital or acquired as a young child. Has been observed especially by Dr. Roger I. Lee over a period of seven years. This case appears to belong to the intermediate group.*

The patient was a woman aged 26. She presented most of the time, some symptoms of purpura hemorrhagica, with diminished blood platelets. She had had numerous attacks of bleeding.

There had been frequently found a leukopenia, usually 3,000, the white count reaching 6,000 to 7,000 after severe hemorrhages. The polynuclears fluctuated between 43 and 68 per cent., the other cells being chiefly normal small lymphocytes.

There had been a chronic, though often slight fluctuating anemia.

This case suggests a greater involvement of white and red cell elements of the marrow than is seen in Case 6 and may possibly be a type of congenital insufficiency of the marrow involving the megakaryocytes especially, the white cells somewhat, and the red cells in a less degree.

CASE 8.—(W. M. 209500.) *A case of leukemia in the nonleukemic phase as shown by the necropsy findings, the diagnosis being made in life by slight enlargement of the lymph nodes and spleen and by the very high lymphocytosis with many abnormal lymphocytes. The purpura hemorrhagica is secondary. The diminution of platelets is due to the crowding out of the giant cells of the marrow by leukemic cells.*

A boy, aged 7 years, began six weeks prior to entrance to lose his appetite and to tire easily. Weakness with night sweats have gradualy increased since and he had grown increasingly pale in the previous four weeks. During the previous week his neck had been swollen and he had had a sore throat, with hemorrhages from his mouth and nose, in the previous three days.

Physical examination showed a pale, poorly nourished boy, with a few purpuric spots, and hemorrhages from his nose and mouth. The tonsils were large and buried; tongue and mouth foul with crusts and exudate; cervical lymph nodes the size of beans and peas; inguinal and axillary nodes easily palpable. The spleen was felt 2 cm. below the ribs. Temperature 103 to 105 F. The patient died three days after entering the hospital.

Blood: Red count 2,000,000 to 1,200,000; hemoglobin, 40 to 50 per cent.? The red cells showed moderate achromia, some variation in size, slight variation in shape, an occasional polychromatophilic and stippled cell, and rarely a blast; reticulated cells 4 per cent. few. The platelets were very few. The white count was 3,400 to 4,200; the polymorphonuclear neutrophils 3 to 4 per cent.; rarely a mast cell. The remaining 96 per cent. of the white cells were lymphocytes, some

54 per cent. of which were abnormal appearing large lymphocytes, some of odd types.

Dr. Wright's important necropsy findings were as follows: A raspberry red marrow which microscopically showed a marked infiltration with cells of the lymphocytic series. There were but few of the normal cells of the marrow, and very rarely was a giant cell found. Other organs of the body also showed infiltrations with cells of the lymphocytic series.

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THE REACTION OF THE CEREBROSPINAL FLUID

PRELIMINARY REPORT ON HYDROGEN-ION CONCENTRATION AS DETERMINED BY THE COLORIMETRIC METHOD *

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The chemical and physical constitution of the cerebrospinal fluid does not furnish any basis for the conception that the reaction of this fluid might be different from that of the blood. The inorganic components,[1] chiefly chlorids, phosphates, and carbonates, occur in almost identical amounts in both the blood serum and cerebrospinal fluid. The organic constituents[2] vary considerably, but are generally less in amount than similar substances in the blood, and the presence of amphoteric amino-acids and proteins would tend to preserve a neutral reaction in this fluid, as emphasized by Robertson.[3] The quantities of these substances, however, do not indicate their influence on the reaction of the fluids in which they occur. Their molecular concentration and ionic dissociation are the important factors. Even the physical properties are approximately the same in both the spinal fluid and blood serum. As measured by cryoscopy, the blood serum (Hammarsten[1]) causes a depression of the freezing point of $\Delta = 0.551$ C. to 0.561 C.; the spinal fluid,[4] $\Delta = 0.566$ C. The normal spinal fluid is equally isotonic with blood serum when tested against red blood corpuscles. In this case, as in that of all body fluids, the hydrogen ion concentration is most intimately related to the dissociable carbonic acid contained in the fluid. The following tabulation, quoted from Mott,[5] gives the generally accepted data on the carbon dioxid content of the spinal fluid.

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* From the Laboratory of Bacteriology and Immunology, Department of Pathology, Johns Hopkins Hospital.

1. Hammarsten: Physiological Chemistry, p. 262. Landau, A., and Halpern, M.: Biochem. Ztschr., 1908, **9**, 72. Zdarek, E.: Ztschr. f. physiol. Chem., 1902, **35**, 201.
2. Cullen, G. E., and Ellis, A. W.: Jour. Biol. Chem., 1915, **20**, 511.
3. Robertson, T. B.: Univ. Calif. Pub. in Physiol., 1909, **3**, 151.
4. Polanyi, M.: Biochem. Ztschr., 1911, **34**, 205.
5. Mott, F. W.: Lancet, London, 1910, **2**, 1 and 79.

	Cerebrospinal Fluid Yield, Per Cent.	Lymph and Serum Yield, by Volume, Per Cent.
By vacuum and heating	10	46
By acid and heating in vacuo	50	50
Difference, representing carbon dioxid in stable combination	40	4

Mott has interpreted these findings to indicate that the carbon dioxid is in more stable combination in the spinal fluid than in the blood. A careful analysis of his procedures, however, throws doubt on the validity of these conclusions. Mott does not give any information about the time elapsing between the withdrawal of the fluid and the determination of its content of carbon dioxid, and his data are insufficient to show whether the 10 per cent. of carbon dioxid per volume obtained by heating in vacuo was more readily or less readily released from the spinal fluid than the 46 per cent. by volume from the blood serum. If, as seems likely from a consideration of the lesser viscosity of the spinal fluid as compared with the blood, this 10 per cent. of carbon dioxid is more subject to escape by diffusion from the spinal fluid, it would have a greater influence on the reaction of this fluid than the more slowly liberated carbon dioxid from the viscous blood serum. It is possible, also, that a major portion of the unstable carbon dioxid of the spinal fluid had escaped before Mott's determinations were begun. The final factor in the relationship between the reaction of the blood and spinal fluid must depend largely on the possibility of an interchange of free hydrogen ions between these fluids. In view of the great diffusibility of the hydrogen ion, it does not seem likely that the choroid plexus and the vascular meninges would obstruct the passage of this ion from the blood into the spinal fluid. Since, therefore, the previous studies on the physical and chemical constitution of the spinal fluid and blood lead to the supposition that the reaction of these fluids should be approximately equal, any reports which point to an opposite conclusion require investigation.

In recent communications, Hurwitz and Tranter,[6] and Weston,[7] say that the hydrogen ion concentration of the spinal fluid averages 8.11, while that of the blood serum, as is well known, ranges normally from 7.6 to 7.8. These authors determined the pH by the colorimetric method of Levy, Marriott and Rowntree, applying the test directly to the spinal fluid and to the dialysate of this fluid. Hurwitz and Tranter, relying on Mott's statement about the stability of the combinations of carbon dioxid in the spinal fluid, apparently made no effort to estimate the hydrogen ion in fluids immediately on their withdrawal from the body, when the interval of time would have the

6. Hurwitz, S. H., and Tranter, C. L.: THE ARCHIVES INT. MED., 1916, **17,** 828.
7. Weston, P. G.: Jour. Med. Research, 1917, **35,** 367.

least influence on the escape of the carbon dioxid. Weston states plainly that his determinations were made on "cerebrospinal fluids sent to the laboratory for the usual routine tests." As we will show later, it is absolutely necessary to carry out the determination on the fluid as soon as it is withdrawn from the spinal canal in order to obtain an estimation of the true reaction.

These authors quote the work of Bisgaard,[8] as a substantiation of their findings. An analysis of Bisgaard's statements, however, does not permit this interpretation. Using a borate mixture with phenolphthalein as an indicator, Bisgaard determined the pH on two spinal fluids immediately on withdrawal of the fluid. On page 62 of his report he writes:[9] "Both spinal fluids proved to be more acid than the most acid borate mixture (5.7 borate + HCl), viz., pH 8.10." On page 64 he concludes:[10] "The hydrogen ion concentration of the spinal fluid is greater than the value of pH = 8.10." He thus clearly states that the spinal fluid was more acid than his borate mixtures, and that he was unable by this method to determine the exact reaction. He also noted that after these same fluids had stood for three hours, the reaction became progressively alkaline, becoming a little over 8.1.

METHOD OF STUDY

The results on which our report is based were obtained by a study of a series of cases at the city hospitals, Bay View Hospital, and at the Johns Hopkins Hospital. In order to classify these spinal fluids more definitely than was permitted by the clinical diagnoses of the cases, they were subjected to the following tests: cell count, globulin-albumin content, Wassermann reaction, colloidal gold test, and refractive index. As will be seen from the cases listed in our tables, a large number of them were psychiatric patients. These tests, however, gave the most positive evidence obtainable that the spinal fluids of many of these patients were normal. On this basis we have classified as normal only those fluids having a cell count below ten, a negative or slightly positive albumin-globulin test by the Ross-Jones and Pandy methods, a negative Wassermann reaction, and only slight changes in the color of the gold solution in Lange's colloidal gold test (Table 2). By these tests the spinal fluids from epileptics were found to be normal. These, however, were grouped in a separate table (Table 4) for the sake of convenience. Other spinal fluids were placed readily in the pathologic categories, of which these tests are the most reliable criteria.

8. Bisgaard, A.: Biochem. Ztschr., 1914, **58**, 1.

9. Beide Spinalflüssigkeiten erwissen sich dadurch saurer als die saurerste Boratmischung (5.7 Borat + HCl), d, h, pH 8.10.

10. Die Wasserstoffionkonzentration der Spinalflüssigkeit ist grösser als die dem Werte pH = 8.10 entsprechend.

It had been thought that the colloidal gold reactions were related to the hydrogen ion concentration of the spinal fluid. These studies soon demonstrated that the precipitation of the gold solution was independent of the reaction of the spinal fluid.

Refractometry was carried out on all the specimens, using an Abbe-Pulfrich direct reading refractometer. With this instrument, the refractive index of normal and pathologic fluids ranged within such narrow limits (1.3348 to 1.3351) that it could not be used as an aid to diagnosis.

TECHNIC

In order to determine definitely the reaction of the cerebrospinal fluid under conditions most closely approximating its state in the body, the tests were applied to the fluid as soon as it was withdrawn by lumbar puncture from the spinal canal. The hydrogen-ion concentration was deterimned by the colorimetric method of Levy, Rowntree and Marriott,[11] directly in the spinal fluid and in its dialysate. The colorimeter used was a standardized instrument prepared by Hynson, Westcott and Dunning under the direction of Dr. Marriott. The pipets and other glassware employed in the tests were thoroughly cleaned and rinsed in triply distilled water. Throughout these tests, tubes of non-sol glass were used, and the water employed was always triply distilled from barium hydrate in the second distillation. The collodion sacs for dialysis were made of Anthony's negative cotton, carefully prepared and tested for leakage.

The procedure was as follows: The spinal fluid was allowed to run from the lumbar puncture needle directly into a large, hard glass test tube and from this it was pipetted into the standard non-sol test tube, 10 mm. inside diameter, for use in the colorimeter. To 1 c.c. of spinal fluid was added 0.1 c.c. of 0.01 per cent. phenolsulphonephthalein in triply distilled water, and this was compared at once with the color standards. The dialysis was performed immediately on 1 c.c. of the cerebrospinal fluid in the collodion sac against 3 c.c. of 0.8 per cent. solution of pure sodium chlorid. After ten minutes, 0.3 c.c. of the indicator were added, and the mixture transferred to a tube of the proper size for the slot in the colorimeter. The alkaline reserve (RpH) was determined according to the method of Marriott,[12] by bubbling through the mixture of spinal fluid and indicator, air purified by passage through sulphuric acid, barium hydrate and calcium chlorid. When a constant color was obtained a reading was taken, from which the alkaline reserve (RpH) was calculated.

Blood was drawn from the arm vein of the patient as soon as the lumbar puncture was completed. Estimations of the hydrogen ion concentration and reserve alkalinity of the blood serum were made, usually within six hours, by the same colorimetric method as that used with the spinal fluids. The inevitable delay in the determinations of the pH of the blood probably accounts for the somewhat low readings which we obtained with these specimens.

In these procedures there are several sources of error. The difference between the shade of color produced when fresh spinal fluid is added to phenolsulphonephthalein and the color standard, makes the comparison somewhat difficult. The fluid assumes an orange tint which has no exact match in the standard tubes. The color intensity, however, allows an approximate comparison to be made. This orange

11. Levy, R. L., Rowntree, L. G., and Marriott, W. McK.: THE ARCHIVES INT. MED., 1915, **16,** 389.

12. Marriott, W. McK.: THE ARCHIVES INT. MED., 1916, **17,** 840.

tint is due to the high content of carbon dioxid in the spinal fluid; it disappears as the carbon dioxid escapes, and reappears on the subsequent addition of carbon dioxid to the fluid. Another source of error is introduced when the spinal fluid is allowed to drop through the air from the lumbar puncture needle and is subsequently pipetted from tube to tube. This exposes a great surface area of the fluid to a gaseous medium in which the carbon dioxid tension is less than that within the body. It is obvious, therefore, that a rapid escape of carbon dioxid will occur at once. The tendency of this loss of carbon dioxid is to render the fluid more alkaline.

To demonstrate the changes in the reaction which occur after the fluid has been withdrawn from the body and allowed to stand in contact with the air, determinations were made at short intervals during six hours. The results of these experiments are summarized in Table 1 and illustrated graphically by Charts 1 and 2.

TABLE 1.—EFFECT OF EXPOSURE TO AIR ON REACTION OF SPINAL FLUID

No.	pH Immediate	Hours After Fluid Obtained									
		¼	½	¾	1	1¼	2	3	4	5	6
21	7.9	7.9	8.0	...	8.0	...	8.1	8.2	8.5	8.6	
29	7.7	7.75	...	...	7.85	...	8.0	8.1	8.2	8.3	
31	7.8	7.8	7.9	7.9	7.9	7.95	8.0	...	...	...	8.6
32	7.75	7.75	7.8	7.85	7.85	7.95	8.1	...	...	...	8.6
33	7.75	7.75	7.75	7.8	7.8	7.9	7.95	...	...	...	8.6
34	7.8	7.8	7.8	7.9	7.9	7.95	8.0	...	...	...	8.6
35	7.7	7.7	...	7.8	...	7.8	8.0	...	...	...	8.6
36	7.75	7.75	...	7.9	...	7.95	7.95	...	...	...	8.6
37	7.75	7.75	...	7.85	...	7.9	8.1	...	...	...	8.5
38	7.8	7.8	...	7.95	...	7.95	8.1	...	...	...	8.4
39	7.9	7.9	...	7.9	...	7.95	8.1	...	...	...	8.4
40	7.7	7.75	...	7.8	...	7.9	8.0	...	...	...	8.6

These tables and graphs show that the reaction becomes progressively alkaline after the fluid has been drawn. That this increasing alkalinity is favored by conditions which permit the ready escape of carbon dioxid and the possible absorption by the fluid of alkaline gases of the air, such as ammonia, is shown by a comparison of the charts. When the fluid is kept in a tube closed by a cork stopper, the reaction changes gradually according to the even diffusion of the gases. When, however, the cork is removed for a short time at different intervals, the reaction changes by sudden stages, as shown by Chart 2. This

emphasizes the necessity of determining the reaction of the fluid as soon as it is obtained, and at the same time explains the false values found by Hurwitz, Tranter and Weston.

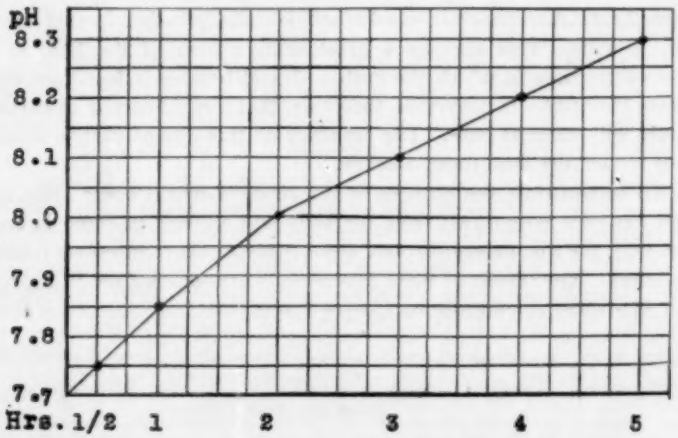

Chart 1.—Spinal Fluid 29-B. Curve shows the increase in alkalinity of spinal fluid kept for five hours in a test tube closed with a cork stopper.

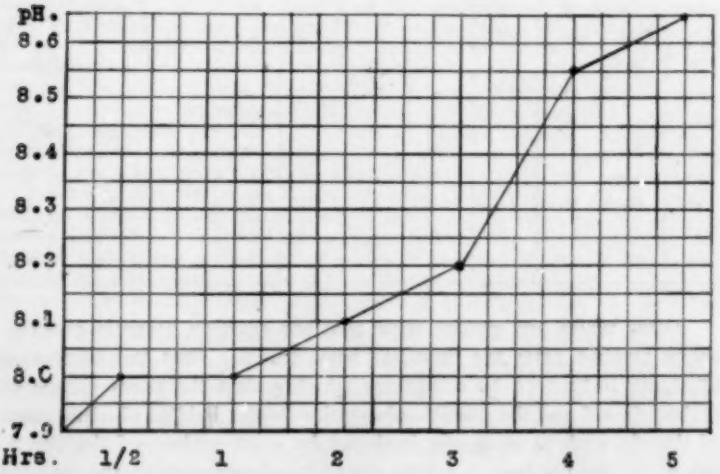

Chart 2.—Spinal Fluid 21-B. This curve shows the increase in alkalinity of the fluid after its withdrawal. The fluid was exposed to the atmosphere of the laboratory at irregular intervals for varying lengths of time. The change in the reaction occurred according to a correspondingly irregular curve.

TABLE 2.—Normal Cerebrospinal Fluids (All Reactions Normal)

Case No.	Diagnosis	Spinal Fluid								Blood-Serum		
		Reac. (Immed.)				Globulin		Wassermann Reaction	Colloidal Gold			
		pH before Dial.	pH after Dial.	RpH	Cells	R-J	Pandy			pH	RpH	Wassermann Reaction
2-Z	Alcoholism	7.9	7.8	8.2	2	0	0	0	1 1 1 0 0 0 0 0 0	7.75	...	0
3-C	Dementia praecox	1.8	7.7	8.2	3	0	0	0	1 1 1 1 1 1 0 0 0	7.9	8.2	0
6-K	Manic depressive	7.8	7.8	8.2	3	0	0	0	0 0 0 1 1 1 0 0 0	7.75	8.4	0
7-O	Narcotism	8.1	7.75	8.2	4	0	0	0	1 1 1 1 1 0 0 0 0	7.75	8.4	0
9-H	Constit. defective	7.8	7.75	8.2	5	0	0	0	1 1 1 1 0 0 0 0	7.7	8.4	0
10-B	Constit. defective	7.9	7.9	8.2	6	±	0	0	0 1 2 2 2 2 1 0 0	7.7	8.4	0
11-B	Manic depressive	7.8	7.8	8.4	...	+	±	0	0 0 1 1 0 0 0 0 0	7.7	...	0
14-E	Homosexualist	7.8	7.7	8.6	2	0	0	0	0 0 1 1 1 0 0 0 0	7.75	...	0
15-S	Dementia praecox	7.85	7.8	8.4	5	0	0	0	1 1 1 1 1 0 0 0 0	7.7	...	0
19-F	Dementia praecox	7.85	7.7	8.4	3	±	0	0	0 0 1 1 1 1 0 0 0	7.7	...	0
21-B	Alcoholism; imbecility	7.9	7.7	...	5	0	0	0	0 0 1 1 0 0 0 0	...	...	0
23-E	Imbecility	7.85	7.8	...	3	0	0	0	0 0 0 1 1 1 0 0 0	...	...	0
25-D	Dementia praecox	7.7	7.7	...	5	0	0	0	1 1 0 0 0 0 0 0 0	...	...	0
27-G	Congenital defective	7.7	7.7	...	4	0	0	0	0 0 1 1 1 0 0 0 0	...	...	0
33-H	Imbecility	7.75	7.65	...	5	0	0	0	0 0 0 0 0 0 0 0 0	7.7	...	0
36-C	Dementia praecox	7.75	7.8	...	4	0	0	0	0 1 1 1 0 0 0 0 0	7.65	...	0
37-G	Melancholia	7.75	7.7	...	10	0	±	0	0 0 0 1 1 1 0 0 0	7.8	...	0
39-M	Dementia praecox	7.9	7.9	...	5	0	0	0	0 0 0 1 1 1 0 0 0	7.7	...	0
40-W	Alcoholism	7.7	7.75	...	8	0	+	0	0 0 0 1 1 1 0 0 0	7.65	...	0
41-G	Dementia praecox	7.95	7.75	...	6	0	0	0	0 0 0 1 1 1 0 0 0	7.85	...	0
42-Z	Paranoia	7.9	7.7	...	4	0	±	0?	0 0 0 0 0 0 0 0 0	7.6	...	0
44-S	Manic depression	7.7	7.75	...	3	+	0	0	0 0 0 1 1 1 0 0 0	7.7	...	0
45-S	Dementia praecox	7.75	7.7	...	5	0	0	0	0 0 0 1 1 1 0 0 0	7.8	...	0
47-B	Dementia praecox	7.8	7.75	...	4	+	0	0	0 0 0 0 0 0 0 0 0	7.8	...	0
48-S	Dementia praecox	7.7	7.75	...	3	0	0	0	0 0 0 0 0 0 0 0 0	7.7	...	0
50-G	Imbecility	7.7	7.7	...	2	0	0	0	0 1 1 1 1 0 0 0 0	7.7	...	0
54-M	Arteriosclerosis; hypertension	7.75	7.7	8.4	3?	+	+0	0	0 0 1 1 1 0 0 0 0	7.75	8.6	0

TABLE 3.—Results of Cerebrospinal Fluid Tests in Senile-Normal Class

Case No.	Diagnosis	Spinal Fluid								Blood-Serum		
		Reac. (Immed.)		RpH	Cells	Globulin		Wassermann Reaction	Colloidal Gold	pH	RpH	Wassermann Reaction
		pH before Dial.	pH after Dial.			R-J	Pandy					
53-T	Hemiplegia (old); arteriosclerosis...	7.7	7.65	8.6	2	++	±	0	0 1 1 2 2 1 0 0 0	7.65	8.4	0
55-G	Amyotrophic lateral sclerosis.....	7.8	7.6	8.6	2	+	+	0	0 1 2 2 2 1 0 0 0	7.8	8.6	0
56-P	Hemiplegia (2 mo.); mitral insuff...	7.8	7.6	8.4	3	++	+++	0	0 0 1 1 1 1 0 0 0	...	...	0
57-T	Friedreich's ataxia.....	7.8	7.7	8.4	4	+	++	0	0 0 1 1 0 0 0 0 0	7.75	8.6	0
58-D	Paget's disease.....	7.75	7.7	8.4	2	+	±	0	0 0 1 1 1 1 0 0 0	7.75	8.4	0
59-B	Chr. bronchitis; arteriosclerosis.....	7.8	7.75	8.6	3	+	++	0	0 1 2 2 2 1 0 0 0	8.0	8.2	0
60-C	Asthma, cardiorenal.....	7.7	7.7	8.6	3	+	++	0	0 0 1 1 1 0 0 0 0	7.85	8.4	0
61-D	Chronic alcoholism.....	7.7	7.65	8.6	5	+	±	0	1 1 1 1 1 0 0 0 0	7.85	8.6	0
62-F	Chr. arthritis; arteriosclerosis...	7.8	7.6	8.4	2	++	++	0	1 1 1 1 1 0 0 0 0	7.9	8.6	0
63-S	Paramyoclonus.....	7.8	7.5	8.6	3	++	++	0	0 0 0 1 1 0 0 0 0	...	...	0
64-K	Cerebral arteriosclerosis.....	7.75	7.7	...	1	+	+	0	0 0 0 1 2 2 2 1 0	...	...	0
65-E	Arteriosclerosis.....	7.65	7.65	8.6	2	++	+	0	0 0 0 0 0 0 0 0 0	7.8	8.4	0
66-S	Chr. infect. arthritis.....	7.7	7.6	8.4	3	+	+	0	0 0 1 1 1 0 0 0 0	7.9	8.4	0
67-W	Hemiplegia (several years).....	7.85	7.7	8.6	2	+	±	0	0 0 1 1 1 1 0 0 0	7.85	8.2	0
68-B	Arteriosclerosis; aortic insuff.....	7.75	7.7	8.6	6	++	+++	0	0 0 1 2 2 2 0 0 0	7.85	8.4	0
69-H	Lateral sclerosis.....	7.7	7.6	8.4	5	++	++++	0	1 1 2 2 2 2 1 0 0	7.85	8.2	0
70-L	Chr. infect. arthritis.....	7.7	7.65	8.4	2	+	+	0	0 1 2 2 1 0 0 0 0	7.9	8.6	0
71-B	Paralysis agitans; Dercum's dis.....	7.7	7.65	8.6	5	+	+	0	0 1 1 1 1 1 0 0 0	7.65	8.4	0
73-R	Chronic arthritis.....	7.75	7.7	8.6	5	±	+	0	1 1 1 1 1 0 0 0 0	...	...	0
75-S	Syringomyelia.....	7.75	7.7	8.6	6	+	+	0	1 1 1 1 1 0 0 0 0	7.7	8.4	0
76-W	Arteriosel.; hemiplegia (recent).....	7.75	7.7	8.4	3							

TABLE 4.—Cerebrospinal Fluid in Epilepsy

Case No.	Diagnosis	Spinal Fluid								Blood-Serum		
		Reac. (Immed.)				Globulin						
		pH before Dial.	pH after Dial.	RpH	Cells	R-J	Pandy	Wassermann Reaction	Colloidal Gold	pH	RpH	Wassermann Reaction
8-H	Epilepsy	7.8	7.7	8.0	4	0	0	0	1 1 1 1 0 0 0 0 0	7.6	8.1	0
24-B	Epilepsy	7.8	7.75	...	4	0	0	0	0 0 0 1 1 0 0 0 0	...	...	0
26-G	Epilepsy	7.7	7.7	...	2	0	0	0	1 1 1 0 0 0 0 0 0	...	...	0
43-B	Epilepsy	7.7	7.7	...	10	0	+	0?	0 0 1 1 2 2 0 0 0	7.7	...	0
49-H	Epilepsy	7.8	7.75	...	4	±	±	0	1 1 1 1 0 0 0 0 0	7.6	...	0
74-T	Epilepsy	7.65	7.6	8.6	4	+	+	0	1 1 1 1 1 0 0 0 0	7.7	8.2	0
77-T	Epilepsy	7.7	7.65	8.4	4	+	0	0	1 1 2 2 1 1 0 0 0	7.8	8.4	0

TABLE 5.—Cerebrospinal Fluid in Syphilis

Case No.	Diagnosis	Spinal Fluid								Blood-Serum		
		Reac. (Immed.)		RpH	Cells	Globulin		Wassermann Reaction, per Cent. +	Colloidal Gold	pH	RpH	Wassermann Reaction, per Cent. +
		pH before Dial.	pH after Dial.			B-J	Pandy					
1-A	Paresis	7.8	7.7	8.2	13	+	±	25	3-3 2 2 1 1 0 0 0	7.7	8.0	50
13-B	Cerebrospinal syphilis	7.75	7.75	8.6	76	++	++	100	5 5 5 4 3 3 1 0 0	7.7	...	100
29-M	Paresis	7.95	7.9	8.4	14	+	+	100	5 5 5 3 1 1 1 0 0	7.8	...	100
29-P	Paresis	7.9	7.8	...	17	++	++	100	5 5 5 5 4 3 1 0 0	...	...	100
29-B	Paresis	7.7	7.7	...	21	++	++	100	5 5 5 5 5 4 3 2 1	...	...	100
30-V	Paresis	7.7	7.7	...	19	+++	+++	100	5 5 5 5 5 5 5 4 3	...	...	100
32-C	Paresis	7.75	7.7	...	16	++	++	100	3 3 3 3 + 4 4 3 2 1	7.8	...	100
72-O	Arteriosclerosis; hemiplegia (old)	7.75	7.7	8.6	12	+++	++	100	4 4 4 4 4 3 2 1 0	7.75	8.4	100
4-S	Dementia praecox; syphilis	8.2	7.7	8.0	0	0	0	50-75 in 1 c.c.	1 1 2 2 2 1 0 0 0	8.0	8.2	0
31-P	Cerebrospinal syphilis	7.8	7.7	...	4	0	0	25?	0 0 1 1 1 0 0 0 0	7.8	...	100
34-T	Paresis	7.8	7.7	...	19	+	++	100	3 3 3 3 + 4 4 3 2 1	7.8	...	100
38-W	Cerebrospinal syphilis	7.8	7.8	...	48	++	++	100	0 0 0 2 3 3 3 2 1	7.8	...	100
51-B	Cerebrospinal syphilis	7.8	7.75	8.4	18	++	++	50 in ¼ c.c.	0 1 2 3 3 2 1 0 0	7.75	8.6	100
5-K	Alcoholism	7.9	7.4	8.2	6	0	0	0	1 1 2 2 2 1 1 1 0 0	7.65	8.1	75
12-K	Syphilis; imbecile	7.8	7.7	8.6	4	±	0	0	0 1 1 1 1 0 0 0 0	7.75	...	75
16-P	Imbecile	7.85	7.8	8.4	Bloody fluid	+	±	0	Bloody fluid	7.7	...	25
17-H	Chronic alcoholism	7.8	7.8	8.4	3	±	±	0	0 0 0 0 0 0 0 0 0	7.7	...	75
18-L	Alcoholism; syphilis	7.8	7.75	8.4	11	±	0	0	0 1 1 1 1 0 0 0 0	7.8	...	100
22-B	Alcoholism	7.8	7.8	...	4	±	+	0	1 1 1 1 0 0 0 0	...	...	100
35-M	Alcoholism	7.7	7.75	...	2	0	0	0	0 0 1 1 1 0 0 0 0	7.8	...	100
52-C	Aortic insufficiency	7.7	...	8.4	5	+	±	0	0 1 1 2 2 2 1 1 1	7.6	8.0	100

RESULTS

Table 2 summarizes the tests on cerebrospinal fluids considered to be normal — having no abnormal reactions. The low hydrogen ion concentration found in Case 7-C was probably due to an error in technic, as the reaction of the dialysate of this fluid was pH = 7.75. The pH of the other fluids included in this table averaged 7.8; the RpH from 0.4 to 0.6; while the pH the RpH of the blood serum in these cases averaged, respectively, 7.75 and 0.5 to 0.8.

Table 3 gives the results of the tests in the cases classifiable as "senile-normal," the fluids having been obtained from patients over 60 years of age. The interesting abnormality in these fluids was the presence of an amount of albumin and globulin precipitable by the Ross-Jones and Pandy tests without coincident increase of cells or decolorization of the colloidal gold. The fluids were otherwise normal, and showed approximately the same pH and RpH as the cases comprising Table 2.

Table 4 contains the group of epileptics. The hydrogen ion concentration of these fluids and the blood serum from these patients were 7.65 to 7.8, as in the normal cases.

Table 5 contains the results of the tests in twenty-one cases of several types of syphilis of the central nervous system, having a positive Wassermann reaction in the blood, spinal fluid, or in both. In the presence of the increased numbers of cells and abnormal amounts of protein in these fluids, the pH varied between 7.7 and 8.2; and 7.4 and 7.9 in their dialysates. This type of pathologic process apparently has no influence on the reaction of the cerebrospinal fluid, and hydrogen ion concentration here is within normal limits.

CONCLUSIONS

These studies allow us to draw the following conclusions:

1. To obtain the true hydrogen ion concentration of the cerebrospinal fluid it is necessary to test the fluid immediately on its withdrawal from the body, avoiding as much as possible exposure to the air.

2. The colorimetric method for determining the hydrogen ion concentration is found to have certain limitations, due chiefly to the peculiar color shades produced by the carbon dioxid content of the spinal fluid. Aside from the differences which may exist between the values of the pH determined by this method and the gas-chain method, the results obtained by the colorimeter have slight inaccuracies, probably equivalent to 0.1 when the hydrogen ion concentration lies between 7.5 and 7.7.

3. When the hydrogen ion concentration of the spinal fluid is determined by the colorimetric method, using phenolsulphonephthalein as the indicator, the values obtained are: average pH of the cerebrospinal fluid = 7.75, with maximum variations of 7.4 to 7.9. The RpH varies from 0.4 to 0.6.

4. This confirms the work of Bisgaard, in which he states that the reaction of the cerebrospinal fluid is more acid than pH = 8.1.

5. The hydrogen ion concentration of the blood serum and of the spinal fluid are approximately equal.

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